Clinical and Developmental Immunology

Perinatal Programming of Childhood Asthma

Guest Editors: Kuender D. Yang, Shau-Ku Huang, and Huey-Jen Su

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Editorial Board

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Editorial

Perinatal Programming of Childhood Asthma

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1. Developmental Origin of Childhood Asthma

Prevalence of childhood asthma has worldwide increased in recent decades. Different genome-wide studies have identified that more than 100 genes in 22 chromosomes were associated with asthma. Different genetic backgrounds in different environments might modulate the susceptibility of asthma. This has been attributed to industrialized environment such as air pollution and microbial-deprivation ecology that polarize the immune response towards allergy sensitization in perinatal stage. Recently, evidence has shown that allergy sensitization may occur in fetal life, and influence of fetal environment may cause epigenetic programming of diseases in adults. Apparently, asthma is not an exception from the Developmental Origins of Health and Diseases (DOHaD), in which both the pre- and postnatal environments could shape the developmental programming of asthma developed in infancy, childhood, and even adulthood.

The association between prenatal environment and disease risk in adults is first demonstrated by Barker showing low birth weight was linked to ischemic heart disease in adult life in 1986 [1], and collaborating with Hales to raise the thrifty phenotype hypothesis emphasizing the importance of developmental plasticity in type 2 diabetes mellitus in 1992 [2]. They also proved that obesity in adults could be traced back to prenatal exposure to famine in the Dutch hunger winter of War World II [3]. Now the prenatal programming of diseases in adults have been linked to a number of chronic diseases including metabolic syndrome, type 2 diabetes, hypertension, cardiovascular disease, schizophrenia, osteoporosis, overweight/obesity, and asthma. Taken together, this suggests that childhood asthma, although heritable, is significantly affected by different environments in perinatal stage.

2. Risk to and Protection from Perinatal Programming of Childhood Asthma

In this special issue, we included 8 papers depicting effects and potential mechanisms of perinatal environments including intrauterine growth trajectory, maternal exposure of cold and herb medication, perinatal exposure to pets, perinatal gut microbiota, bottle feeding, genetic determinant of cockroach allergy, interaction of parental atopy and genes, and gene-environment interactions on the development of asthma. These papers together have highlighted different epigenetic and genetic effects of perinatal environments and parental genetic backgrounds on the perinatal programming of asthma. As summarized from these articles and shown in Figure 1, maternal (prenatal) environments have a strong impact on the programming of childhood asthma in which folic acid supplement, parental smoking, oxidative stress, and cold and herb medication are risk factors to childhood asthma. In newborn and infant stage, prematurity, vacuum delivery, skewed (high or low) birthweight, and bottle feeding are risk factors to childhood asthma. In toddler stage, early daycare placement, antibiotic uses, and parental smoking are also associated with childhood asthma. The environmental programming of asthma in perinatal stage is likely mediated via epigenetic modification or immune differentiation toward a higher T-cell type 2 (Th2) response or a lower Treg differentiation. For instance, we found that maternal atopy interacting with the CTLA-4 gene polymorphisms for antenatal IgE production begins in prenatal stage [4], and miRNA-21 underexpression in neonatal leukocytes,

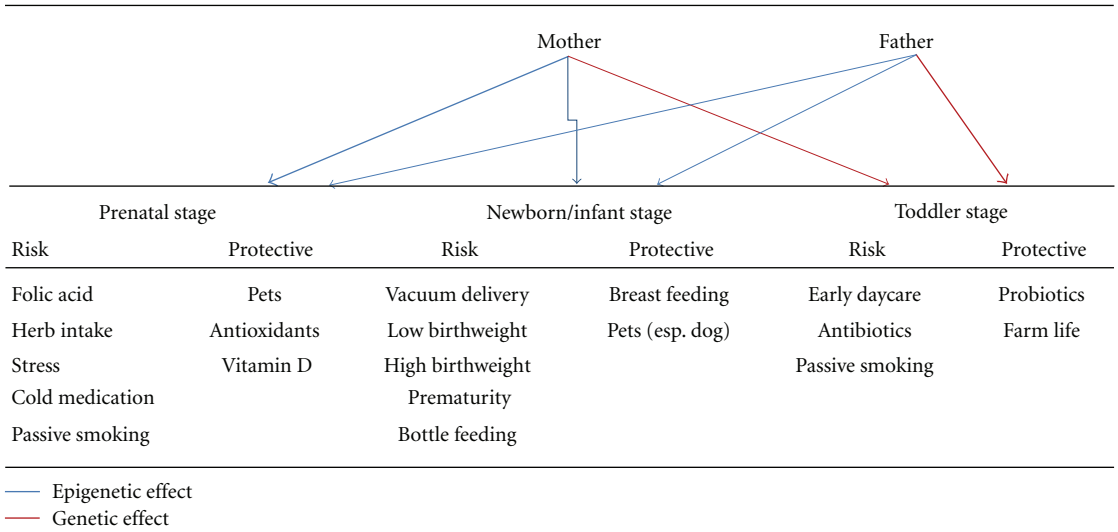

Figure 1: Summary of environmental (epigenetic) and genetic programming of asthma.

which is correlated to overexpression of TGFR expression, is associated with allergic rhinitis in childhood [5]. Recently, our preliminary studies on prenatal tobacco exposure found that 37 DNA CG sites in 30 genes of neonatal leukocytes have greater than 10% increase or 10% decrease in its CG methylation contents associated with parental tobacco smoke, and the CG methylation contents in certain genes' promoter have a significant interaction for the development of asthma and allergic rhinitis in childhood [6]. On the other hand, paternal influence on the development of asthma occurs in later childhood, suggesting genetic effects on the development of allergic sensitization are also important in children exposing to aeroallergens, pollution, and complementary foods beyond infancy. Fortunately, not all perinatal factors are risk to the development of childhood asthma, certain perinatal factors may contribute to protection from the development of asthma. Prenatal exposure to pets, vitamin D supplement, or antioxidants such as Mediterranean diet is shown to be protective from the development of asthma. In postnatal stage, breastfeeding, intake of probiotics, and growing up in farms [7] are associated with less risk to allergy.

3. Future Perspectives

Another review article on whether perinatal diets such as vitamins, polyunsaturated fatty acid, protein-hydrolyzed infant formula, or the time and types of complementary foods are protective from the development of asthma is not included in this issue because of its complex controversy and the paper submitted for this issue was not good enough for publication. Neither the hygiene hypothesis for the development of asthma nor the persistence and remission of childhood asthma in adolescents are included in this issue. This guest editor team including K. D. Yang, MD, PhD, from the Department of Medical Research and Development, Show Chwan Health Care System, Taiwan; S.-K. Huang, PhD, from Johns Hopkins Asthma Center, Johns Hopkins University, Baltimore, USA; H.-J. Su, PhD, from Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan; J. Abe, M.D., Ph.D., from the Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo, Japan anticipates that another issue of perinatal programming of asthma including advances in the knowledge of DOHaD depicting influence of nutrition and hygiene on the development and remission of asthma will come not far in order to provide a prospect for early prediction and prevention of childhood asthma.

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Review Article

Perinatal Gene-Gene and Gene-Environment Interactions on IgE Production and Asthma Development

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Atopic asthma is a complex disease associated with IgE-mediated immune reactions. Numerous genome-wide studies identified more than 100 genes in 22 chromosomes associated with atopic asthma, and different genetic backgrounds in different environments could modulate susceptibility to atopic asthma. Current knowledge emphasizes the effect of tobacco smoke on the development of childhood asthma. This suggests that asthma, although heritable, is significantly affected by gene-gene and gene-environment interactions. Evidence has recently shown that molecular mechanism of a complex disease may be limited to not only DNA sequence differences, but also gene-environmental interactions for epigenetic difference. This paper reviews and summarizes how gene-gene and gene-environment interactions affect IgE production and the development of atopic asthma in prenatal and childhood stages. Based on the mechanisms responsible for perinatal gene-environment interactions on IgE production and development of asthma, we formulate several potential strategies to prevent the development of asthma in the perinatal stage.

1. Introduction

Atopic asthma is a complex disease associated with IgE-mediated allergic reactions. Most allergens elicit IgE antibodies, which bind to mast cells; when cross-linked, the mast cell releases inflammatory mediators that cause bronchospasm and mucus formation [1]. Nonatopic asthma refers to inflammation and constriction of the airways that are not caused by exposure to an allergen. As with numerous ill-defined diseases in which numerous extrinsic influences and genetic factors contribute to onset of the disease, the term "complex disease" is applied. Such terminology refers to asthma as caused by a complex relationship between genetic and environmental components, resulting in the clinical manifestations of atopic asthma. Systemic administration of humanized anti-IgE antibodies causes a 95–99% decrease in serum IgE, along with anti-inflammatory feature of asthma [2], which supports the IgE-mediated mechanism of atopic asthma. Numerous genome-wide association (GWA) studies have identified more than 100 genes in 22 chromosomes associated with atopic asthma [3, 4]. Moreover, genetic backgrounds and environmental exposures could modulate susceptibility to asthma [5, 6]. This suggests that asthma, although heritable, is significantly affected by environmental factors. Evidence has recently shown that molecular mechanisms of atopic disease may not be limited to DNA sequence differences, but also gene-environmental interactions for epigenetic difference and/or regulatory T cells (Treg) [7, 8]. We describe recent advances in our understanding based on the mechanisms responsible for gene-gene and gene-environment interactions on IgE production and development of atopic asthma in the perinatal stage.

Table 1: Gene-gene interactions on IgE production and asthma phenotype.

Total IgE levels/ asthma phenotype		Gene-gene interactions
Prenatal	IgE levels (cord blood, infant blood)	*CD86-VTCN1* [9]
		IL13-CCL17 [10]
		IL1RL1-BPI [11]
		TGFBR2-IL2RA [12]
		IL13-CCL17-CXCL10 [10]
		MD2-ITGB2-BPI [11]
Childhood	IgE levels	*CD14-AOAH* [13]
		IL1RL1-NOD1 [11]
		IL13-IL4RA [14, 15]
		IL13-IL13RA1 [16]
		IL13-TARC [17]
		TLR2-TGFBR2 [12]
		MD2-MAP3KIP2-BPI [11]
		TLR2-IL6RA-IL2RA [12]
	Asthma	*CD14-AOAH* [13]
		CD274-LILRA4 [9]
		GSNOR-B2AR [18]
		IL4-IL4RA [19]
		IL6-IL6R [20]
		IL13-IL4R [21]
		IL13-IL4RA [15, 17, 22]
		LTA4H-ALOX5AP [23]
		SOCS1-MAP3K7IP1 [11]
		TNC-NPSR1 [24]
		EPHX1-CYP1B1-CYP2D6 [25]
		IL2RA-FOXP3-IL2RA [12]
		IRAK1-NOD1-MAPK7IP1 [11]
		STAT6-STAT4-IFNG [26]
		TLR2-IL2RA-TGFBR2 [12]
		B2AR-CCR3-CysLTR1-FCER1B [27]
		INSIG2-IL4-CHIA-ADIPOQ-ALOX5 [28]
		IL4-STUB1-ADRB2-IL4RA-IL13RA2-CHIA [28]

2. Gene-Gene Interactions on IgE Production and Asthma Development

Allergic diseases, including atopic asthma, have long been attributed to IgE-mediated reactions, and elevation of serum IgE levels has been correlated to allergic diseases [29, 30]. Allergic sensitization might occur *in utero* and be related to the future development of allergic diseases [31, 32]. Elevation of cord blood IgE (CBIgE), although not sufficient to predict the development of allergic diseases in childhood [33, 34], was shown to be a risk predictor for the development of aeroallergen sensitization [35] and for later development of childhood asthma [36]. Significant associations with elevation of CBIgE levels were reported previously for *cytotoxic T-lymphocyte-associated protein 4* (*CTLA4*) +49A allele [37] and for *IL13, CCL17,* and *CXCL10* gene interactions [10].

Reijmerink et al. [11] used the multifactor dimensionality reduction (MDR) analysis, which is designed to translate high-dimensional genetic data into a single dimension, to explore the gene-gene interactions on IgE production and the development of asthma. Interactions between these genes, located in the Toll-like-receptors- (TLR-) related pathway, showed that the polymorphisms in *interleukin 1 receptor-like 1* (*IL1RL1*) and *bactericidal/permeability-increasing protein* (*BPI*) were the optimal model of interaction using 2-way MDR analysis ($P = 0.02$) to predict the elevation of total IgE levels. The polymorphisms in *myeloid differentiation factor* (*MD*)*-2, beta-2 integrin* (*ITGB2*), and *BPI* were identified as the optimal model of the 3-way MDR analysis ($P = 0.01$) to predict the elevation of total IgE levels at 1 to 2 years of age.

A number of gene-gene interactions implicating a link between IgE production and the development of asthma in the perinatal stage are shown in Table 1, in which more complex interactions among different immune genes are found in asthma than in IgE production. Moreover, a kinetic change of different gene profiles associated with IgE production was found in children with increasing ages. In our studies on Chinese cohorts, IgE production in infancy and toddlerhood was associated with immune and remodeling genes, and IgE production in preschool age was associated with MHC class II antigen genes, such as *HLA-DPA1* and *HLA-DQA1* (our unpublished data). These results suggest that altered immune remodeling in infancy and toddlerhood may prime children for allergic sensitization in childhood, depending on HLA genotypes.

With the introduction of powerful novel genetic-analysis tools, the heritable component of asthma has gained increasing attention over the last decade. This attention calls for open approaches to the linkage and GWA studies rather than traditional candidate gene approaches to the genetics of asthma. The main strength of GWA studies lies in their ability to discover genuinely novel disease-candidate genes, especially those associated with moderate risks [38]. In a recent GWA study for asthma, Moffatt et al. genotyped more than 317,000 single-nucleotide polymorphisms (SNPs) in 994 patients with childhood asthma and 1243 people without asthma, and identified that polymorphisms of *ORM1-like 3* (*ORMDL3*) on chromosome 17q21.1 were strongly associated with childhood asthma [39]. The association was also independently replicated in 2320 participants from a cohort of German children and in 3301 participants from the British 1958 birth cohort [39].

ORMDL3 appears to be a gene in a very old part of the human genome, and similar genes were found in primitive organisms such as yeast. Although the transcript level of *ORMDL3* is strongly correlated to susceptibility to childhood asthma, its role remains unclear. Additional GWA studies on asthma are underway, and cross-validation data among these studies may lead to better conclusions on the responsible genes for the development of asthma.

3. Gene-Environment Interactions on IgE Production and Asthma Development

Increasingly, more studies in the literature identify novel genes associated with asthma and suggest that numerous genes with small effects rather than few genes with strong effects contribute to the development of asthma. These genetic effects may in part differ with respect to a patient's environmental exposures. Several environmental factors, such as maternal atopy, endotoxin, tobacco smoke, pollutants, allergens, cold air, microbial infections, medication, and exercise, are known to exacerbate asthma symptoms [40–44]. Of these environmental factors, maternal atopy, microbial exposure, and tobacco smoke exposure are particularly important and its gene-environment interactions are described below.

3.1. Maternal Atopy. Allergy sensitization may occur in fetal life. Moreover, the immature immune system is highly susceptible to immunomodulatory environmental conditions, particularly in the prenatal and postnatal periods [45]. Maternal atopy may impact neonatal immune development and subsequently alter the allergic responses of neonates. A number of candidate gene studies investigating interactions between maternal atopy and airway hyperresponsiveness have also been performed for 3 main groups of genes: immunity genes (*CD14, IL13, CCL22,* and *CTLA4*), the stress gene (*fibroblast growth factor 1* (*FGF-1*)), and the MHC class I antigen gene (*HLA-G*) gene. Specifically, maternal but not paternal atopy has a significant impact on CBIgE elevation, depending on the gender and *CTLA4* +49A/G polymorphism of newborns [46]. Maternal atopy interacting with the polymorphisms in *IL13* and *CCL22* genes was reported to be a good predictor of CBIgE elevation [10]. In contrast, in the absence of maternal atopy, the *CTLA4* +49GG genotype in female newborns had a protective effect on CBIgE elevation [46].

3.2. Microbial Exposure. The prevalence of asthma is widely skewed in developed and developing countries, the reasons for which remain obscure. The hygiene hypothesis has emerged as a popular explanation. The hygiene hypothesis was initially developed to explain a reduced rate of allergic diseases among children with older siblings [56]. The underlying concept is that an increased exposure to microbes and their products during the perinatal stage protects against the development of allergic responses to common environmental antigens, such as dust mites, fungi, cockroaches, and pollens. Although abundant epidemiological studies support the hygiene hypothesis, significant inverse relations between exposures to these compounds and atopy and asthma have been found.

Protection from allergies is conferred by children growing up on small farms in parts of Europe [57], supporting this hypothesis. The specific exposure responsible for the protection against allergies afforded by this rural lifestyle is unknown, but most of the results have focused on germs and their endotoxin, which can be measured in house dust. Endotoxin, a component of the cell walls of Gram-negative bacteria, is one of the pathogen-associated molecular patterns (PAMPs). PAMPs, evolutionarily highly conserved structural components of microbes, are recognized by conserved receptors of innate immune systems, pattern-recognition receptors (PRRs), the human CD14, TLRs, nucleotide-binding oligomerization domain (NOD)-1, NOD2, and C-type lectin receptors. Because the specific agent responsible for the protective effect against asthma in children with a rural upbringing is unknown, the exposure metric in some studies on gene-environment interaction on IgE levels, allergies, or asthma in children growing up on farms relies on self-reported contact with germs and other animals, as listed in Table 2.

Table 2: Interactions of genes with maternal atopy, endotoxin and other environmental factors on IgE production and asthma phenotype.

		Environment factors-gene interaction
Prenatal	Cord blood IgE levels	Maternal atopy-*FGF1* [10]
		Maternal atopy-*IL13*-*CCL22* [10]
		Maternal atopy-gender-*CTLA4* [46]
		Endotoxin-*CD14* [47]
Childhood	IgE levels	Animal contact-*CD14* [48]
		Helicobacter pylori-*CD14* [49]
		Endotoxin-*CD14* [50]
		Day care attendance-*CD14* [51]
		Day care attendance-*IL4R* [51]
	Asthma	Country living-*CD14* [52]
		Fungi-*CHIT1* [53]
		Maternal bronchial hyperresponsiveness-*HLA-G* [54]
		Children of farmer-*TLR2* [55]

The relationship between endotoxin exposure and IgE levels seems to be affected by a common SNP in the promoter region of *CD14*, a receptor involved in endotoxin recognition [50]. A significant gene-environment interaction exists between the *CD14* −260C/T genotype and endotoxin exposure on $CD4^+$ lymphocyte numbers, particularly $CD4^+Foxp3^-$ lymphocytes at 1 year of age [47]. Interactions of *IL13* with *IL4R*, *IL13R*, or *CCL17*, as well as the interactions of *CD14* with daycare attendance, endotoxin, or rural living affect IgE production and the development of asthma in childhood [14–17, 21, 22, 50–52].

3.3. Tobacco Smoke Exposure. Previous studies have provided evidence on the role of tobacco smoke exposure (TSE) as a determinant risk factor of childhood asthma [40, 75, 76]. Recent studies suggest that *in utero* TSE from maternal smoking during pregnancy is associated with reduced lung function and constitutes a significant risk factor for the development of asthma [75, 77–81]. This parent-of-origin

Table 3: Interactions of genes with perinatal environmental TSE and pollution on asthma development.

Stage	Environment factors-gene interaction
Prenatal	TSE-Chromosome 1q43-q44, 4q34 and 17p11 [58]
	TSE-*ADAM33* [59]
	TSE-*B2AR* [60]
	TSE-*GSTM1* [5, 61]
	TSE-*GSTP1* [62]
	TSE-*IL1RN* [63]
	TSE-*IL13* [64]
	Pollution-*ACSL3* [65]
	TSE and pollution-*TGFB1* [66]
Childhood	TSE-Chromosome 3p and 5q [67]
	TSE-Chromosome 1p, 1q, 5q, 9q and 17p [68]
	TSE-Chromosome 1q43-q44, 4q34 and 17p11 [58]
	TSE-*B2AR* [69]
	TSE-*CD14* [70]
	TSE-*GSTP1* [71]
	TSE-*GSTM1* [71]
	TSE-*TNF* [72]
	Pollution-*GSTM1-TNF* [73]
	Pollution-*GSTP1-TNF* [73]
	Pollution-Catalase genes-Myeloperoxidase genes [74]

effect points to a significant role of the maternal prenatal environment on later asthma risk in the offspring [82]. Early postnatal TSE from parents was also associated with infant wheezing and lower respiratory tract infections and increased the prevalence of asthma independently from the effect of *in utero* TSE from maternal smoking during pregnancy [83]. Moreover, the effect of current TSE is known not only to influence the severity of asthma, but also to impair the efficacy of inhaled corticosteroid treatments [84]. Although exposure to active and passive cigarette smoking is a well-recognized risk factor for the development of asthma, asthma manifests in only a portion of people [85, 86]. Furthermore, Jaakkola et al. showed that a combination of parental atopy and TSE has a synergistic effect on the risk of childhood asthma [85]. This suggests that the effect of environmental factors on the development of asthma can be modified by genetic constitution.

A number of candidate gene studies investigating interactions with TSE have been performed for 3 main groups of genes: innate-immunity genes (*CD14, tumor necrotic factor* (*TNF*), and *IL-1 receptor antagonist* (*IL1RN*)), adaptive-immunity genes (*IL13* and *transforming growth factor* (*TGF*)-*β1*), and response and remodeling genes (*a disintegrin and metalloprotease domain-containing protein* (*ADAM*)-33, *glutathione S-transferase* (*GST*)-*M1, GSTP1*, and *β2-adrenergic receptor* (*B2AR*)), as shown in Table 3. Timing of exposure to TSE is also an important consideration in the analysis of gene-environment interactions on the development of childhood asthma. In the prenatal stage, the *IL1RN* gene polymorphism rs2234678 GG genotype significantly increased the relative risk of asthma only in children of mothers who smoked during pregnancy [63]. Reijmerink et al. showed that *ADAM33* polymorphisms increased the risk of developing asthma *in utero*, but postnatal TSE did not [59]. A GWA study demonstrated that the chromosomes 3p and 5q were linked to childhood asthma in tobacco-exposed families [67]. Wang et al. [69] showed that the joint effect of the *B2AR* polymorphism at position 16 with TSE increased the risk of asthma in a dose-dependent manner. Some genes were only associated with asthma in the presence of TSE [63, 64]. In *GSTM1*-null children of school age, *in utero* exposure to smoking is associated with an increased prevalence of early-onset asthma, asthma with current symptoms, persistent asthma, lifetime history of wheezing, wheezing with exercise, wheezing requiring medication, and number of emergency department visits in the past year in comparison to children with the $GSTM1^{+}$ genotype [61, 87, 88].

A recent study showed a synergistic effect of air pollution levels and functional SNPs within catalase and myeloperoxidase on the respiratory-related school absence of asthmatic children [74]. The exposure-traffic air pollutants also increased the effect of *TGFB1* −509C/T polymorphism on the development of asthma [66].

4. Environmental Influence of Epigenetic Programming for IgE Production and Asthma Development in the Postnatal Stage

Epigenetic programming is broadly defined as heritable changes in gene expression or cellular phenotype other than changes in DNA sequences [95, 96]. Epigenetic alterations are believed to occur not only prenatally or shortly after birth, but also during later developmental periods, influencing gene expression differentially throughout the lifespan. Although GWA studies hold promise for identifying unexpected gene-environment interactions, how the gene-environment interactions affect IgE production and asthma development remains unclear. One of the potential mechanisms is the epigenetic programming of asthma by gene-environment interactions in the perinatal stage. Early-life dietary supplementation and environmental exposures are known to affect adult metabolism and phenotype through alterations in DNA CG methylation [97].

Several environmental exposures reportedly interact with genetic predisposition through epigenetic mechanisms on total IgE levels and asthma phenotype (Table 4). Hollingsworth et al. are the first to report an increased risk of allergic disease in *in utero* dietary methyl donors because of the differential methylation of 82 genes [90]. One of these is *runt-related transcription factor 3* (*Runx3*), a gene known to downregulate allergic airway inflammation; it is associated with decreased transcriptional activity and mRNA expression in lung tissue. DNA methylation levels of *Runx3* increased in animals exposed to methyl donors *in utero* [90]. This effect could be transmitted to subsequent progeny mice. *Runx3* is known to cooperate with T-bet in the silencing of IL-4 in Th1 cells [98]. A reduced Runx3 level might lead to enhanced transcription of IL-4 skewing toward Th2

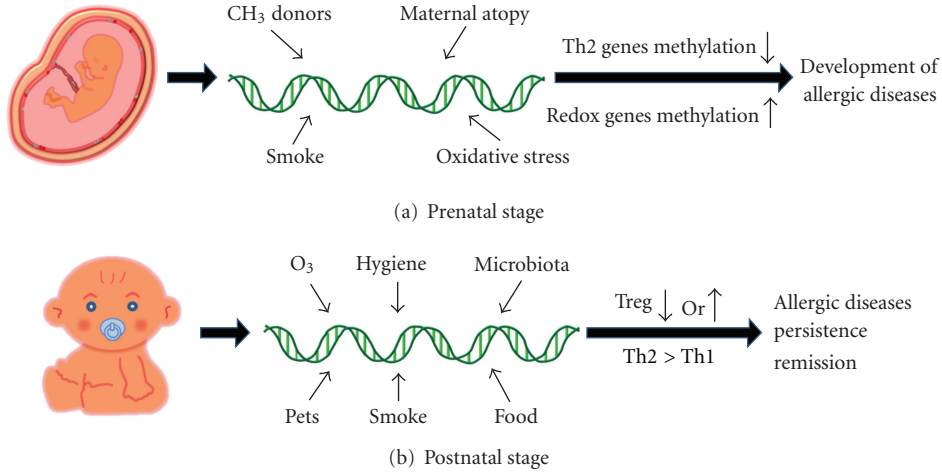

Figure 1: Mechanisms of pre- and postnatal environmental factors on the development of asthma. A number of prenatal factors such as maternal diet with methyl donors, maternal atopy, TSE, and oxidative stress could alter the epigenetic programming of Th2 and redox genes, resulting in the allergic sensitization and diseases (a). Additional postnatal environmental conditions such as pollution, secondhand TSE, pets exposure, infant diets and microbiota may modulate or drive the expression of Treg and/or Th1/Th2 genes resulting in skewed or balanced Th2 responses that contribute to persistence or remission of allergic diseases (b).

Table 4: Environmental modification of epigenetic program on IgE production and asthma.

Phenotypes	Environment factors-epigenetic modification
IgE levels	High-fat (HF) intake-obesity [89] *murine*
	Maternal diet with methyl donors-82 loci [90] *murine*
	Aspergillus fumigatus-diesel exhaust particles (DEP)-*IL4* promoter [91] *murine*
	Aspergillus fumigatus-diesel exhaust particles (DEP)-*IFNG* promoter [91] *murine*
Asthma	Folic acid supplements in pregnancy [92]
	A lwoffii F78-*IFNG* promoter [93] *murine*
	Maternal diet with methyl donors-82 loci [90] *murine*
	Pollution-*ACSL3* [65]
	Microbial exposure-*IFNG* [94]

differentiation, as observed in anti-$CD3^+CD28^+$ antibody-stimulated $CD4^+$ lymphocytes. Although the significance of epigenetic inheritance in humans is unclear, one recent study reported that folate supplements in pregnancy are associated with increased childhood wheezing [92]. In contrast, 2 cohort studies showed that dietary pattern during pregnancy was not associated with recurrent wheezing [99] or asthma and related outcomes [100].

Maternal smoking in pregnancy may feasibly impact the development of allergic airway disease through epigenetic pathways because of changes in DNA methylation or histone modifications. Air pollution has been also linked to epigenetic changes in *ACSL3* [65]. Similarly, diesel exhaust particles were shown to affect CG methylation of *IL4* and *IFNG* promoters, which are involved in airway inflammation [91].

5. Implications of Gene-Environment Interactions on Prevention of Asthma

IgE production and asthma are not controlled by a single gene, but are involved in a complex interaction with environmental modification of genetic and epigenetic programming of asthma. Any individual study is unlikely to be able to account for all of the complex interactions with confounding factors in prenatal and postnatal stages and from other host factors such as maternal diets, obesity, and gender. Despite these limitations, the study of environmental epigenetics promises to help us understand the theoretically preventable disease, asthma. Environmental changes can epigenetically modulate Th2 and redox genes in the prenatal stage and change the Treg function and/or skewed Th2 immune reaction in the postnatal stage, as shown in Figure 1. Notable differences in the immune responses of allergic and nonallergic children are evident *in utero*, where environmental exposures such as maternal diet with methyl donors, maternal atopy, TSE, and oxidative stress could alter the epigenetic programming of Th2 and redox genes, resulting in allergic sensitization and diseases (Figure 1(a)). Additional postnatal environmental conditions such as pollution, secondhand TSE, pet exposure, infant diets, and microbiota may modulate or drive the expression of Treg and/or Th1/Th2 genes, resulting in skewed or balanced Th2 responses that contribute to persistence or remission of allergic diseases (Figure 1(b)). Based on the mechanisms responsible for the perinatal epigenetic and immune regulation of the development and remission of allergic diseases, we may be able to formulate potential strategies

to prevent the development of asthma in the perinatal stage by manipulating perinatal conditions such as diet control or complementary food and by early screening of DNA methylation changes followed by modulation of CG methylation levels.

6. Conclusion

Increasingly, more evidence suggests that different gene-environment interactions play an important role on IgE production before and after birth. We conducted a systematic review of recent studies to identify the roles of gene-gene and gene-environmental interactions on the prenatal and childhood IgE production, as well as the development of asthma. Prevention of IgE production and IgE-mediated diseases may be possible by controlling different environmental factors for patients with susceptible genotypes early in the perinatal stage. Control of maternal atopy in pregnancy and modulation of gene expression such as *CTLA4* and *IL13* may be a target for decreasing antenatal IgE production and possibly lowering perinatal allergy sensitization. TSE is a well-recognized risk for the development of childhood asthma; reducing the perinatal exposure of tobacco smoke may prevent the development of asthma, particularly in subjects carrying susceptible Th2 and redox genotypes. Further studies are necessary to compare gene-gene and gene-environment interactions on IgE production and asthma development in different ethnic populations and to study whether manipulations of maternal diets or postnatal complementary food could modulate epigenetic programming of asthma.

Author's Contributions

Jen-Chieh Chang and Lin Wang contributed equally to this study.

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Review Article

Perinatal Programming of Childhood Asthma: Early Fetal Size, Growth Trajectory during Infancy, and Childhood Asthma Outcomes

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The "fetal origins hypothesis" or concept of "developmental programming" suggests that faltering fetal growth and subsequent catch-up growth are implicated in the aetiology of cardiovascular disease. Associations between reduced birth weight, rapid postnatal weight gain, and asthma suggest that there are fetal origins to respiratory disease. The present paper first summarises the literature relating birth weight and post natal growth trajectories to asthma outcomes. Second, issues regarding the interpretation of antenatal fetal ultrasound measurements are discussed. Finally, recent reports linking antenatal measurement and growth trajectory to early childhood asthma outcomes are discussed. Understanding the nature and timing of factors which influence antenatal growth may give important insight into the antecedents of early-onset asthma with implications for interventions.

1. Introduction

As a rule, mammals either have a short gestation and are born in an immature condition or have a long gestation but are mature at term and can run or swim shortly after birth. One exception to this rule is *Homo sapiens* who has a relatively long gestation but is still immature at term. There is therefore a relatively large window of opportunity for both antenatal and early post natal exposures to positively or negatively affect human development. The respiratory system provides one example of human development spanning across antenatal and post natal periods since the airways are established before the pregnancy reaches midpoint but alveoli start to appear during the third trimester through to at least three years of age [1]. Not unsurprisingly therefore, antenatal and post natal exposures have been implicated in the causation of respiratory disease.

Describing the impact of antenatal and post natal exposures on development of the respiratory system is relatively easy after birth and methods include symptom-based questionnaires and physiological measurements. In contrast, determining the effect of antenatal exposures on the individual's respiratory wellbeing *in utero* is considerably more challenging. To date, birth weight has been commonly used as an index of fetal wellbeing and the assumption is that adverse exposures on the respiratory system are manifest as reduced growth. However, birth weight is the end point of nine month's growth and, as Figure 1 demonstrates, insults at different gestations might result in "catch-up growth" associated with high birth weight (outcome 1, Figure 1), normal birth weight (outcome 2, Figure 1), or low birth weight (outcome 3, Figure 1). For humans, the timing of a fetal insult and ensuing catch-up growth is not yet fully described, but the suggested growth trajectories depicted in Figure 1 can be inferred from animal studies [2] and also observational studies in humans [3, 4]. Growth acceleration may also (theoretically) be a primary phenomenon, that is, not a response to fetal growth failure. What is required is insight into fetal wellbeing during antenatal life and how this is relevant to post natal outcomes. Recently, longitudinal cohorts have been established which are able to link fetal ultrasound measurements made during pregnancy to post natal outcomes [4–9]. These studies are able to explore the fetal origins hypothesis, also termed developmental programming [10–12], which proposes that "fetal undernutrition in middle to late gestation, leads to disproportionate fetal growth,

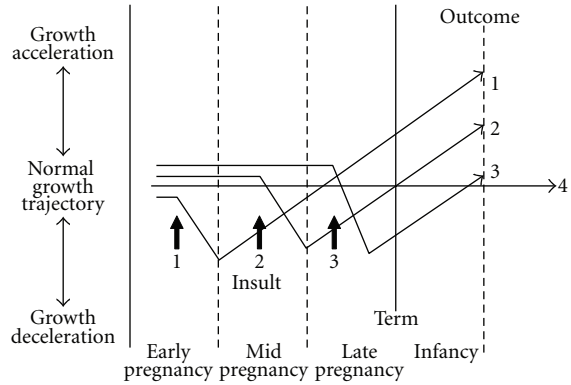

Figure 1: Schematic diagram demonstrating how growth deceleration at different gestations with resulting "catch-up growth" may result in low, normal, or high birth weight. Insult 1 in early pregnancy results in initial growth deceleration followed by growth acceleration during mid and late pregnancy and post natal life and is associated with increased birth weight (Outcome 1). Insult 2 occurs during mid pregnancy and results in growth deceleration followed by growth acceleration during later pregnancy and infancy, associated with normal birth weight (Outcome 2). Insult 3 occurs during late pregnancy leading to with low birth weight and ensuing "catch-up growth" during infancy (Outcome 3). Outcome 4 illustrates normal growth throughout pregnancy and infancy.

programs later (coronary heart) disease" [10]. The present review considers the relationship between fetal growth and childhood asthma, the latter being an example of a chronic condition where exposures in fetal life are thought to be important to aetiology. The review has three aims.

(i) To summarise recent evidence linking birth anthropometry and growth during infancy to respiratory outcomes.

(ii) To explore the potential and limitations for using fetal ultrasound measurements as an index for fetal wellbeing.

(iii) To describe the recent literature linking fetal size, fetal growth trajectories, and respiratory outcomes in later life.

2. Birth Anthropometry and Respiratory Outcomes

There is a considerable literature relating birth size to asthma symptoms in later life but no systematic review. There is a systematic review summarising the literature relating gestation to asthma [13] where the consensus is that a shorter gestation at delivery is associated with increased risk for the later development of asthma. For the purpose of the present article, key words "Asthma" and "Birth weight" were used in an Ovid search engine (to yield 129 abstracts) and relevant papers published since 2000 were reviewed. Publications known to the author but not identified by the search were added (see Table 1). A formal systematic review on this topic is required.

A number of themes emerge from this semistructured literature review. First, there is no consensus on the relationship between birth weight and asthma; nine studies find an inverse relationship [14–22], ten find no relationship [23–32], and three find a positive relationship [33–35]. There may be an issue of power since inverse relationships are seen in large and very large study populations (median of 8071 individuals) whereas studies reporting no effect tend to be of medium size (median number of participants 3628). Second, there is more consistent evidence of increased asthma among those of low birth weight (i.e., less than 2.5 kg) where there is approximately a doubling in risk for asthma; it is not clear whether this is independent of prematurity. Third, there is limited evidence of increased asthma among very heavy infants (i.e., >4.5 kg) [33, 34]. Finally, other indices of size at birth, for example, ponderal index [30, 35] (weight/length^3), may be more closely related to asthma compared to birth weight.

Given the different growth trajectories which may converge to a given birth weight (Figure 1) it is perhaps not surprising that the relationship between birth weight and asthma is not straight-forward. Using birth weight as a "snap shot" of fetal wellbeing has its limitations and in recognition of this, post natal growth trajectory has been related to asthma.

3. Post Natal Weight Gain, Asthma, and Lung Function

Post natal growth trajectory may be a more accurate reflection of antenatal growth compared to birth weight; a movie picture rather than a photograph telling a story. For example, an infant born on the 9th centile for birth weight who demonstrates accelerated post natal growth and reaches the 50th centile by three months might be assumed to have had growth suppression *in utero*. In contrast, a similar-sized infant born on the 9th centile whose post natal growth follows the 9th centile is simply marginally smaller than average and most likely grew along the 9th centile *in utero*. Ideally antenatal and post natal growth trajectories would be obtained to study the relationship between early growth and asthma outcomes.

What is important when understanding the relevance of the relationship between somatic and pulmonary growth is that whilst the body may be able to "catch up," the airways are established by mid pregnancy and may not be able to catch up, leaving the individual with small airways relative to body size. Proof-of-concept for dysanapsis (i.e., dissociation between somatic and pulmonary growth) comes from a cohort study of 1232 individuals from Chile study where increased gain in weight and length during infancy were associated with a modest increase in asthma symptoms at age 23–29 [36]. Studies where followup is only reported into childhood also find positive associations between weight gain during infancy and asthma risk. A cohort in Southampton reported that increased weight and adiposity (but not length) during infancy was associated with increased risk for wheeze at of age three years [7]. Paul and colleagues [37] used data collected as part of a randomised

Table 1: Summary of studies linking birth weight to asthma.

Study reference	Year of birth	Country	Asthma Outcome	Age at follow up	Number in cohort	Positive or negative	Magnitude of effect*
[21]	1928–1952	Sweden	Doctor diagnosed asthma, asthma admission or death	36–70 years	21,588 twins	Negative	OR for 2 kg 1.58 [1.06, 2.38] compared to 2.5 kg
[27]	1947–1973	Nordic-Baltic countries	Wheeze, wheeze with shortness of breath	20–47 years	1683	No association	Wheeze reduced by 2% [±19%] for each 500 g wt gainBirth weight 2500 versus 4000 g linked with 8% increase in FEV1
[32]	1966	Finland	Doctor diagnosed asthma ever and symptoms in last 12 months	31 years	4719	No association	Using ponderal index tertiles and middle as reference, risk for asthma in lowest 1.14 [0.78, 1.65] and for highest 1.22 [0.85, 1.75]. Ponderal index had significant U-shaped relationship with skin prick positivity
[15]	1970–1989	UK	Hospital admission for asthma	2–10 years	248612 recruited 4017 admitted	Negative	Risk increased 20% [10–30] comparing 1–3 kg versus 3–4 kg
[30]	1975–1979	Finland	Life time prevalence doctor-diagnosed asthma	16 years	3065 twin pairs	No association	OR 0.61 [0.30, 1.24] for 2.5–3 kg versus <2 kg. OR highest versus lowest quartile for ponderal index (wt/length^3) 1.82 [1.18, 2.79]
[26]	1975–1988	UK	Asthma diagnosis	13–14 years	10,809	No association for birth weight	Highest versus lowest quintile head circumference increased hay fever (1.23 [1.03, 1.47]). Highest quintile birth wt increased hayfever (1.17 [0.99, 1.39]). Highest versus lowest birth weight 0.92 [0.62, 1.35]
[25]	1977–1980	Australia	Asthma	Mean 14 years	180 preterm and 42 term deliveries	No association	Asthma prevalence 21% in controls, 21% in 1–1.5 kg birth wt and 15% in 0.5–1 kg birth wt
[35]	1984–1987	Denmark	Hospital admission for "definite" or "any" asthma	12 years	10440	Positive	Definite asthma increased 1.62 [1.02, 2.59] for above compared with below average birth weight. More convincing relationship between increasing ponderal index and any and definite asthma admission
[34]	1985–1988	Canada	Emergency visits for asthma	10 years	83,595 children	Positive above 4.5 kg	Above 4.5 kg increased risk (1.16 [1.04, 1.29]) compared to normal weight. Beyond 4.5 kg 10% increase risk [2, 19].

Table 1: Continued.

Study reference	Year of birth	Country	Asthma Outcome	Age at follow up	Number in cohort	Positive or negative	Magnitude of effect*
[33]	1986	Finland	Doctor diagnosed asthma	16	9479	Positive at very highest weight	Highest birth wt (>4.51 kg) had greatest atopic asthma risk 2.4 [1.33, 4.32] compared to 2.5–3.34 kg
[16]	1987	Finland	Hospitalisation or free entitlement to asthma medication	7 years	60254	Negative	Birth wt < 2.5 kg OR for asthma 1.83 [1.50, 2.24] independent of maternal smoking
[14]	1988	USA	Physician diagnosed asthma by age 3 years	0–4 years	8071	Negative	<1.5 kg OR 2.9 [2.3, 3.6], 1.5–2.5 kg OR 1.4 [1.1, 1.8] compared to ≥2.5 kg
[23]	1988–1990	Netherlands	Parent reported asthma	Mean 6 years	1961	No association for birth weight	Relationship between asthma and gestational age (risk for >36 weeks 2.0 [1.0, 4.0] compared to 40 weeks) and asthma and head circumference : birth weight ratio (risk for above median 1.8 [1.1, 3.2] compared with below median).
[20]	1992–1998	Sweden	Ever had asthma	9–12 years	446 twins	Negative	OR 1.57 [1.38, 1.79] for each kg decrease
[28]	1994–1996	Sweden	Wheeze	4 years	2869	No association for birth weight	Birth length ≥ 90th centile OR any wheeze 0.4 [0.21, 0.77]
[29]	1994–1996	USA	Physician diagnosed plus wheeze in the last year	6 years	454 at risk for asthma	No association	Birth weight < 2.5 kg OR asthma 1.05 [0.40, 2.73]. Gestation < 38.5 weeks assoc with increased asthma (OR 4.7 [2.1, 10.5])
[17]	1994–2000	Denmark	History of asthma	3-9 years	8280 twin pairs	Negative	Asthma assoc with 122 g lower birth weight [85, 160]. Risk increased by 4% per 100 g wt reduction
[31]	1995–2001	Canada	Hospital admission or >1 physician visits with asthma over 2 years	6	687,194	No association	Extremely heavy (>6.5 kg) OR 1.21 [0.67, 2.19]
[22]	Approx 1995–2001	USA	?	1–5 years	2410	Negative	Linear 20% increase risk [2, 35] for each kg reduction in birth weight. Breast feeding apparently protective of influence of low birth weight
[24]	1996-1997	Netherlands	Doctor diagnosed	Mean 7 years	3628	No association	Relationship between birth weight and wheeze (risk increased by 17% [1, 35] for each kg reduction in birth weight
[18]	1996–2004	Finland	Asthma diagnosis and prescribed inhaled steroids or montelukast	Three years	20,623 case-control pairs	Negative	Birth weight < 2.5 kg OR 1.40 [1.20, 1.60]
[19]	1998–2000	USA	Asthma diagnosis	3	1803	Negative	Birth weight < 2.5 kg OR 2.36 [CI not given]

* OR=odds ratio for asthma. Numbers in square brackets correspond to 95% confidence intervals.

controlled trial of inhaled corticosteroids in wheezy 2-3-year-old children and related change in weight between birth and enrolment to asthma outcomes including burden of symptoms, quality of life, functional capacity, exacerbations of asthma and medication side effects. Compared with reduced growth, accelerated growth was associated with a 50% increase in exacerbations requiring prednisolone treatment (0.6/year/child versus 0.9/year/child) and more than a 100% increase in unscheduled physician visits (0.5/year/child versus 1.1/year/child). Although there is a relative paucity of data linking growth in infancy to asthma diagnosis and symptoms, this limited literature is entirely consistent. The literature linking weight gain and pulmonary function is less consistent.

In infancy, rapid early weight gain is associated with reduced $FEV_{0.4}$ at one month [38] and reduced mid expiratory flow at the end of infancy [39] but a trend for increased mid expiratory flow at age 11 years [39]. In a large cohort study in the Avon region of UK, infants with birth weight < 10th centile who demonstrate catch-up growth had evidence of better lung function as 7-8 year olds compared to those of a similar weight who do not catch up but still lower than peers of average birth weight [40]. The improved lung function in the "catch-up" group was not significantly better than the persistently small infants despite this being a very large study population and the results could be interpreted as supporting the concept of dysanapsis or possibly indicating that catch up in somatic growth may be associated with very small degree of catch up in pulmonary growth [40].

Cohorts with followup into adulthood have demonstrated increased weight gain during infancy being associated with increased lung function in adults, that is, a reversal of the relationship seen between weight gain and lung function in infancy. For men aged 31 years, this was equivalent to a mean increase of 51 mLs FVC for each kg gained and for women, mean increases of 19 mLs FEV1 and 30 mLs FVC [41]. In a second study increased growth during first three years was associated with increased functional residual capacity and gas transfer at 32 years of age [42] but not with altered FEV_1. The transformation of the association between post natal growth and lung function from negative in infants to positive in adults is difficult to understand but might be a cohort effect, that is, the nature of the relationship has changed over time.

Findings from these epidemiological studies could be interpreted as follows.

(i) A more rapid increase in size during infancy is associated with increased risk for asthma.

(ii) A more rapid increase in size during infancy is associated with reduced lung function during infancy but marginally increased lung function during adulthood.

4. Application of Fetal Measurements to Epidemiological Studies

Ultrasonography provides a unique view of the developing fetus, and in many countries ultrasound examinations are routinely carried out to date pregnancies in the first trimester (usually at approximately week 10) and detect congenital abnormalities during and after the second trimester (approximately week 20). The interpretation of fetal measurements in the context of post natal outcomes is not necessarily straightforward and there are a number of methodological considerations each of which apparently weaken any relationship between fetal size and later health outcomes.

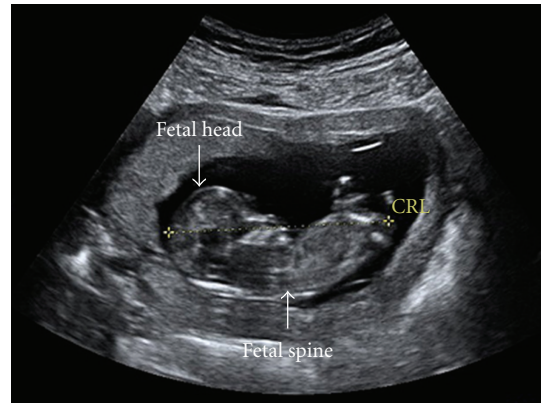

Figure 2: Ultrasound image of a 12-week fetus. The broken yellow line is the crown rump length (CRL) measurement.

First, different measurements are made at different gestations, so which measurement is "best"? Crown rump length (Figure 2) is measured in the first trimester to date a pregnancy and is known to be a very accurate predictor of gestation in the first trimester [43] but becomes more variable beyond 14 weeks [43] and other measurements are required. Second trimester fetal measurements include biparietal diameter [44], femur length [45], and abdominal girth [46] and are not routinely measured in the first trimester since the fetus is so small. Even modern ultrasound may lack precision for head, abdominal, and limb measurements in a ten-week fetus which on average measures 45 mm from crown to rump. At birth, weight, crown-heel length, and occipitofrontal circumference can be measured but these are not directly comparable to first and second trimester measurements. Unfortunately, there is no single "gold standard" fetal measurement which can be made throughout pregnancy. Second, even in health, fetal growth is not linear over time [47] and an apparent acceleration or deceleration may be normal. Third, in the context of fetal "stress" there is sparing of head growth at the expense of the body which leads to asymmetrical growth retardation; in the context of fetal "stress," the fetal head measurement may be within the normal range but the abdominal girth will be reduced. Fourth, as with all measurements there is an element of interobserver variability and first trimester fetal measurements, this is estimated to be approximately 10% [48]. In epidemiological studies, the impact of factors such as nonlinear growth and intrasubject variation in measurements can be minimised by inclusion of large numbers of participants.

Finally, and perhaps most importantly, anthropometric measurements are not necessarily related to the function

Table 2: Summary of asthma and allergy outcomes in the context of changing growth trajectory during early pregnancy.

First-second trimester	Increased rate of growth			Reduced rate of growth		
	Asthma symptoms	Atopy	Lung function	Asthma symptoms	Atopy	Lung function
Southampton 3 years		Increased skin prick positivity		Increased nonatopic wheeze		
Aberdeen 5 years	Increased asthma		Reduced FEV_1, FVC, $FEF_{25–75}$			Reduced FEV_1
Aberdeen 10 years	Increased asthma	Increased hayfever	Reduced $FEF_{25–75}$	Increased asthma	Reduced eczema	Reduced FVC

Table 3: Summary of asthma and allergy outcomes in the context of changing growth trajectory during late pregnancy.

Second-third trimester	Increased rate of growth			Reduced rate of growth		
	Symptoms	Atopy	Lung function	Symptoms	Atopy	Lung function
Southampton				Increased atopic wheeze	Increased skin prick positivity	
Aberdeen 5 years	Increased asthma*					
Aberdeen 10 years	Increased asthma		Reduced FEV_1 and FVC			

* Data not published but can be confirmed by the author.

of individual organ systems, for example, cardiovascular system. However, spirometry is positively correlated with anthropometric measurements in children including sitting height [49] (i.e., crown rump length) and limb length [50] (i.e., femur length) and therefore it is biologically plausible that fetal measurements are a valid index of respiratory function.

5. Fetal Growth Trajectory and Asthma and Allergy Outcomes

At the time of writing, fetal growth has been related to childhood asthma outcomes in three reports from two cohorts [7, 9, 51]. Methodological differences between the two cohorts make direct comparison difficult but there are some patterns which emerge (Tables 2 and 3).

In a cohort recruited in Southampton [7], prospective fetal measurements were made at 10, 19, and 34 weeks gestation. The same fetal measurements were made on each assessment, that is abdominal and head circumference, and this allows relative change in the same measurement to be studied. The Southampton group have focussed on relative change in growth and have not yet reported associations between absolute fetal size and childhood asthma outcomes. In their paper, Pike et al. [7] report an association between reduced head circumference growth between weeks 10 and 19 and reduced growth in abdominal girth between weeks 19 and 34 and increased wheeze at age three. Contrasting associations between fetal growth trajectory and atopy at age three years were seen; increasing abdominal growth between 10 and 19 weeks but reduced growth of the same parameter between weeks 19 and 34 were linked to increased risk for atopy. Although based on a very young group of individuals, these findings provide proof-of-concept that factors which influence antenatal growth may be important to asthma and atopy. Additionally these findings may explain the inconsistent association between asthma and atopy, for example, increased growth in early pregnancy may increase atopy but reduce asthma risk whereas faltering growth in later pregnancy may be associated with both.

A second cohort, recruited in Aberdeen [9, 51], was primarily designed to relate dietary exposures to childhood asthma outcomes and fetal measurements from routine first trimester "dating" and second trimester "fetal anomaly" ultrasound examinations were retrieved retrospectively. This meant that not all fetal measurements could be retrieved and different fetal measurements were made in the first and second trimester, whilst third trimester measurements were those made at delivery, that is, birth weight, length, and head circumference. Strengths of the Aberdeen cohort include relatively extended followup at ages five and ten years, inclusion of physiological measurements in childhood (e.g., spirometry), and relation of absolute fetal size to asthma outcomes. The Aberdeen group have also looked at some maternal factors which affect fetal growth [8, 51].

At five years of age, the main message from the Aberdeen cohort was that reduced fetal size in the first trimester was associated with increased risk for asthma symptoms and obstructed lung function regardless of later fetal growth [51]. Those who were initially short and then became larger had worse asthma outcome compared to those who were persistently large. To place fetal measurements into context, the average fetus measured 46 mm at ten weeks and asthma risk at five years fell by an average of 5% for each mm increase in size.

As part of the evaluation of the Aberdeen cohort at age five years, fetal size was related to maternal diet and smoking during pregnancy. Reduced first trimester fetal size was

associated with reduced maternal plasma alpha tocopherol (vitamin E) suggesting that maternal diet may be important to early asthma causation [51]. The concept that vitamin E may enhance fetal lung growth is supported by work in animal models [52, 53] but it is also possible that increased vitamin E is merely an index of a generally healthier maternal diet during pregnancy and a single nutrient is not likely to have a considerable impact on fetal growth in isolation. Additional factors associated with fetal growth were male gender which was associated with increased growth during first and second trimesters [51] and maternal smoking, which was associated with reduced femur length [8]. There are a number of mechanisms whereby maternal smoking may affect fetal and lung development. Carbon monoxide, a by-product of tobacco smoking, induces fetal hypoxia [54] which may directly induce fetal growth failure. Products of tobacco smoke can indirectly affect fetal growth via a negative influence on placental function [55]; for example, nicotine causes vasoconstriction in placental vessels [55]. Maternal smoking may also reduce fetal growth by suppression of placental growth hormone and fetal insulin-like growth factor endocrine function [56]. Finally, and not to the exclusion of the previous mechanisms, maternal (and also perhaps grandmaternal smoking) may induce epigenetic in the developing fetus which could increase the unborn child's risk for asthma in later life [57].

At ten years of age, the main message from the Aberdeen cohort remained that reduced first trimester fetal size was linked to a poorer asthma outcome. Asthma outcomes were worst in those who were persistently small, best in those who were persistently large, and intermediate for those with changing growth trajectories. Additionally, the investigators demonstrated that reduced first trimester fetal size was associated with asthma which was present at both ages five and ten years but not transient or later onset asthma symptoms. Birth weight and first trimester fetal size were independently associated with reduced lung function at ten years suggesting that an element of remodelling of the respiratory system may be taking place throughout pregnancy. At ten years, but not at age five years, there was evidence that increased early growth was associated with hayfever and reduced early growth was apparently protective for eczema; there was no association between changing growth trajectory and skin prick positivity at ten years.

Putting the results of the two cohorts together is not straightforward due to the differences in methodology, analytical approach and age at follow up, however some broad conclusions can be drawn. First, changes in fetal growth trajectory size do appear to influence the risk for childhood asthma symptoms; for both cohorts reduced early growth was associated with increased asthma symptoms (Table 2). In later pregnancy, the Aberdeen group report increased asthma associated with increased growth in late pregnancy but in contrast, the Southampton group observed growth failure was associated with increased symptoms (Table 3). Second, early growth acceleration was associated with increased risk for atopy and atopic conditions in both cohorts; interestingly this pattern is the opposite predicted by the Barker hypothesis [10] but this was proposed for cardiovascular outcomes and not atopy. Other cohorts in Australia and Netherlands can shortly be expected to report on asthma and associated outcomes in the context of fetal growth and these will be welcome additions to the present literature. What is clear is that factors which influence fetal size and growth are important to childhood asthma outcomes and antenatal interventions may prevent childhood asthma, for example, by influencing maternal diet or smoking.

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Research Article

Feeding Bottles Usage and the Prevalence of Childhood Allergy and Asthma

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This study aimed to examine the association between the length of use of feeding bottles or pacifiers during childhood and the prevalence of respiratory and allergic morbidities. A large-scale questionnaire survey was performed in day care centers and kindergartens (with children's ages ranging from 2 to 7 years) in southern Taiwan, and a total of 14,862 questionnaires completed by parents were finally recruited for data analysis. Effects of using feeding bottles on children's wheezing/asthma (adjusted OR: 1.05, 95% CI 1.00–1.09), allergic rhinitis (adjusted OR: 1.04, 95% CI 1.00–1.08), and eczema (adjusted OR: 1.07, 95% CI 1.01–1.2) were found. Moreover, significant dose-dependent relationships were further established after an adjustment for confounders was performed that included children's ages, gender, gestational age, birth weight, length of breastfeeding, the age when first given infant formula or complementary foods, family history, parental educational levels, and smoking status, as well as the problem of indoor water damage. This study was the first to reveal the potential risk of using plastic consumer products such as feeding bottles on the reported health status of preschool children in Asian countries.

1. Introduction

Because of the multifactorial nature of pathogenesis, it is much clearer now that the rising prevalence and morbidity of childhood asthma and allergic diseases cannot be explained only by genetics and allergen exposure. Several chemicals from many common consumer products have been shown to have toxicity in animal studies and have also been suggested to have an impact on human health. For example, bisphenol A (BPA) is used to manufacture polycarbonate plastic and epoxy resins, which are used in a large number of products found indoors, such as epoxy, building components, and electronic equipment as well as protective coatings on food containers and baby bottles. Toxicological studies of animals have suggested that exposure to BPA is associated with morphologic, functional, and behavioural anomalies related to reproduction. Phthalate esters are stabilizers and plasticizers in commonly used consumer products [1] such as personal care products, food packaging, medical equipment, toys, and building materials. Experimental studies during the past decade have proposed their role as an adjuvant on T_H2 differentiation or as having an association with the early phases of inflammatory response [2, 3].

We are commonly exposed to various chemicals with potential health concerns in our daily lives through the use of consumer products; however, there have been no studies attempting to verify whether the use of these kinds of products is associated with health status, especially in the case of the most susceptible group, young children. The current analysis was aimed at an examination of the association between the length of use of pacifiers or feeding bottles during childhood and the prevalence of respiratory and allergic disease/symptoms in a Taiwanese population.

2. Materials and Methods

2.1. Study Subjects. In 2005 and 2006, randomly selected kindergartens ($n = 201$) and day care centres ($n = 259$)

in the Greater Tainan metropolitan area of southern Taiwan were asked through telephone interviews to participate in a questionnaire survey aimed at identifying the relationship between indoor environmental quality in the home to children's health. An average of 73% of the successfully contacted schools ($n = 335$) agreed to participate and to help send a questionnaire to the parents of children between the ages of 2 and 6 who attended their schools. A total of 14,862 questionnaires were returned with a 68% response rate of questionnaires sent to the 355 kindergartens and day care centres. The study was approved by the Human Experiment and Ethics Committee at National Cheng Kung University Hospital in Tainan, Taiwan.

2.2. Questionnaire. Questions for assessment of the children's asthma and allergy were adopted from the International Study of Asthma and Allergies in Childhood (ISAAC) protocol [4], including the following questions.

Core question for wheezing and asthma.

(i) Has your child *ever* had wheezing or whistling in the chest at any time in the past?

(ii) *In the last 12 months*, has your child had a dry cough at night for more than two weeks, apart from a cough associated with a cold or chest infection?

(iii) Has your child been diagnosed with asthma by a doctor?

Core question for allergic rhinitis.

(i) In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu?

(ii) Has your child been diagnosed with hay fever or allergic rhinitis by a doctor?

Core question for eczema.

(i) Has your child ever had an itchy rash (eczema), which was coming and going for the last 6 months?

For the environmental condition component used on the questionnaire for this study, questions that were identical to the worldwide Dampness in Buildings and Health (DBH) study [5] were adopted. Questions regard to the length of use of pacifiers or feeding bottles in the survey were as follows.

(i) Did your child use a pacifier? If yes, at what age did your child stop using it?

(ii) Did your child use a feeding bottle? If yes, at what age did your child stop using feeding bottles?

There were eight options for answering either question, including "(1) never used, (2) stopped use before 1 year old, (3) stopped use before 2 years old, (4) stopped use before 3 years old, (5) stopped use before 4 years old, (6) stopped use before 5 years old, (7) stopped use before 6 years old, and (8) is still using."

2.3. Data Analysis. Differences in the percentages between any of the groups shown in Table 2 were calculated using a chi-square, while the P value for trends was applied using a chi-square for the trend test (ordinary by ordinary) for ordinal data. Multivariable logistic regression was applied to examine the effect after adjusting for potential confounders. All statistical analysis was performed with the SPSS, version 17 (Chicago, IL, USA).

3. Results

Questionnaires were mostly filled out by mothers (62.3%). Table 1 presents the characteristics of 14,862 children, including their ages, gender, gestational age, birth weight, length of being breastfed, the age first given infant formula or complementary foods, family history, parental educational levels, and smoking status. Moreover, a high prevalence of reported water damage in the home (35.7%) was shown in southern Taiwan.

The lifetime prevalence of parental reporting of wheezing/asthma, allergic rhinitis, and eczema among preschool children is tabulated in Table 2. The average prevalence of doctor-diagnosed asthma, doctor-diagnosed allergic rhinitis and the reporting of eczema symptoms during the 6 months prior to this study among preschool children in Taiwan was 9.3%, 19.3%, and 17.6%, respectively. More than half of the children studied (50.8%) had rhinitis symptoms, including sneezing or a runny or blocked nose when they were absent resulting from having had a cold or a flu in the previous 12 months. The highest rate of diagnosed asthma was found at the age of 5 years old, at 10.2%. Moreover, it was apparent that the prevalence of allergic rhinitis and reported symptoms was increasing along with the age of children, whereas an inverse situation was found for eczema. As to the morbidities of wheezing/asthma and rhinitis, children with any one of related symptoms or diseases were recognized as cases. Overall, there were 34.9% and 53.6% of preschool children with reported morbidities of wheezing/asthma and allergic rhinitis, respectively, in Taiwan.

With regard to clinical data, physician-diagnosed health statuses of young children, especially in the case of asthma, were not stable and permanent until the age of 3 years. The current analysis therefore excluded subjects who were younger than 3 years old ($n = 489$, Table 1) and those missing age information ($n = 1700$, Table 1). The length of using pacifiers or feeding bottles among the study children was stratified into a quartile range as shown in Table 3. A total of 24.3% children never had used feeding bottles or had used them until they were 2 years old; 25.3% children had stopped use between 2 and 3 years old; 24.2% children had stopped use between 3 and 5 years old; the remaining 26.2% of the children had used these items until the time of this investigation. Results revealed that the prevalence rates of wheezing/asthma, allergic rhinitis, and eczema in the four groups were increasing significantly (P value for trend <0.05), with higher quartiles representing a longer length of using feeding bottles among the children who were subjects in this study. The only statistically significant trend between outcomes and

Table 1: Characteristics of study children.

	n (%)	*n* (%) of missing data*
Questionnaire filled out by		*1,030* (*6.9*)
Both father and mother	3,022 (21.8)	
Mother only	8,619 (62.3)	
Father only	1,738 (12.6)	
Grandparents	216 (1.6)	
Others	237 (1.7)	
Age		*1,700* (*11.4*)
Less than 3 years old	489 (3.7)	
3 years old	1,631 (12.4)	
4 years old	3,740 (28.4)	
5 years old	5,021 (38.1)	
6 ~ 7 years old	2,281 (17.4)	
Gender		*2,278* (*15.3*)
Female	6,101 (48.5)	
Male	6,483 (51.5)	
Gestational age		*521* (*3.5*)
Before week 32	205 (1.4)	
In week 32–36	2,178 (15.2)	
In week 37–42	10,731 (74.8)	
In week 43 or later	745 (5.2)	
Unknown	482 (3.4)	
Birth weight		*230* (*1.5*)
Less than 2500 grams	932 (6.4)	
2500–4200 grams	13,376 (91.4)	
More than 4200 grams	180 (1.2)	
Unknown	144 (1)	
Breastfed totally or partly until		*279* (*1.9*)
Never	5,630 (38.6)	
Younger than 3 months	6,087 (41.7)	
3–6 months	1,371 (9.4)	
Older than 6 months	1,495 (10.3)	
The age first given infant formula		*969* (*6.5*)
Never	248 (1.8)	
Younger than 3 months	9,739 (70.1)	
3–6 months	2,568 (18.5)	
Older than 6 months	1,338 (9.6)	
The age first introducing complementary foods		*590* (*4*)
Never	111 (0.8)	
Younger than 3 months	220 (1.5)	
3–6 months	5,761 (40.4)	
Older than 6 months	8,180 (57.3)	
Ever had allergic symptoms to foods		*449* (*3*)
Unknown	1,022 (7.1)	
Never	11,947 (82.9)	
Yes, ever had allergic reaction to	1,444 (10.0)	
seafood	768 (53.1)	
milk or dairy products	269 (18.4)	

Table 1: Continued.

	n (%)	*n* (%) of missing data*
eggs	233 (16.1)	
peanuts	136 (9.4)	
fish	124 (8.6)	
fruit	101 (7.0)	
soya, peas, beans	48 (3.3)	
vegetables	44 (3.1)	
nuts, almond	43 (3)	
flour	34 (2.4)	
others	376 (26.1)	
Family history		*424* (*2.9*)
Paternal asthma	310 (2.1)	
Paternal allergic rhinitis or eczema	2,709 (18.8)	
Maternal asthma	408 (2.8)	
Maternal allergic rhinitis or eczema	2,733 (18.9)	
Sibling with asthma	643 (4.4)	
Sibling with allergic rhinitis or eczema	2,361 (16.4)	
Paternal educational levels		*336* (*2.3*)
Junior and junior high school	2,348 (16.1)	
Senior high school	5,943 (40.9)	
Undergraduate degree	5,216 (35.9)	
Graduate degree	1,019 (7)	
Maternal educational levels		*369* (*2.5*)
Lower than junior high school	2,117 (14.6)	
Senior high school	6,510 (44.9)	
Undergraduate degree	5,476 (37.8)	
Graduate degree	390 (2.7)	
Parents smoked during the child's first year of life		*627* (*4.9*)
Either father or mother smoked	6,303 (49.7)	
Indoor problems with water damage		*215* (*1.7*)
In any room of the home	3,205 (35.7)	

* The percentage of missing data among 14862 subjects.

Table 2: Prevalence of diseases or symptoms among study children.

	Total population, % (*n*)	Stratified by the age of child while questionnaire survey, % (*n*)					
		Less than 3 years old	3 years old	4 years old	5 years old	6 ~ 7 years old	*P* value*
Wheezing/asthma							
Wheezing ever	28.6 (4090)	33.9 (161)	31.8 (507)	28.3 (1020)	27.6 (1325)	28.3 (618)	**0.002**
Cough at night last 12 months	11.2 (1611)	11.3 (54)	12.5 (198)	11.1 (404)	10.7 (518)	10.5 (232)	0.326
Doctor-diagnosed asthma	9.3 (1176)	6.2 (27)	8.6 (120)	8.7 (282)	10.2 (437)	9.6 (184)	**0.021**
Any one of the abovementioned	*34.9* (*5146*)	*39.0* (*190*)	*38.3* (*623*)	*34.5* (*1283*)	*33.8* (*1685*)	*33.9* (*766*)	***0.002***
Allergic rhinitis							
Rhinitis last 12 months	50.8 (7301)	44.2 (212)	49.5 (786)	49.1 (1778)	51.7 (2517)	53.9 (1187)	<**0.001**
Doctor-diagnosed rhinitis	19.3 (2791)	12.6 (60)	16.6 (265)	19.6 (716)	20.3 (992)	21.2 (470)	<**0.001**
Any one of the abovementioned	*53.6* (*7906*)	*46.9* (*229*)	*51.9* (*843*)	*52.6* (*1957*)	*54.4* (*2714*)	*56.7* (*1280*)	<***0.001***
Eczema							
Eczema during last 6 months	17.6 (2539)	29.2 (140)	19.9 (318)	17.4 (635)	16.4 (798)	16.3 (361)	<**0.001**

* *P* values were calculated by Pearson Chi-Square to compare the difference of percentages among five age groups.

Table 3: The association between the length of using feeding bottles or pacifiers and childhood allergic and respiratory morbidities.

% (*n*)	Quartile of using length for feeding bottles or pacifiers				*P* value†	*P* value for trend‡
	<25th percentile	25th–50th	50th–75th	>75th percentile		
Length of using feeding bottle						
Range of quartile	*Never used and stopped use before 2 yrs, 24.3 (2979)*	*Stopped use between 2 and 3 yrs, 25.3 (3103)*	*Stopped use between 3 and 5 yrs, 24.2 (2960)*	*Used until now, 26.2 (3205)*		
Wheezing/asthma	33.0 (976)	34.8 (1076)	34.2 (1007)	37.5 (1199)	**0.002**	**0.001**
Allergic rhinitis	52.3 (1550)	54.4 (1680)	54.1 (1594)	55.4 (1768)	0.102	**0.025**
Eczema	15.6 (452)	17.1 (516)	16.1 (467)	19.7 (620)	**<0.001**	**<0.001**
Length of using pacifiers						
Range of quartile	*Never used, 27.7 (3433)*	*Stopped use before 1 yr, 27.0 (3345)*	*Stopped use between 1 and 2 yrs, 25.5 (3162)*	*Stopped use between 2 and 6 yrs as well as used until now, 19.9 (2465)*		
Wheezing/asthma	33.0 (1129)	36.1 (1202)	35.1 (1104)	35.4 (869)	**0.050**	0.084
Allergic rhinitis	51.6 (1764)	55.2 (1834)	55.4 (1745)	54.1 (1328)	**0.007**	**0.025**
Eczema	16.5 (555)	16.9 (550)	17.3 (537)	17.8 (428)	0.636	0.194

† *P* values were calculated by Pearson Chi-Square to compare the difference of percentages among four quartile groups.
‡ *P* values for trend were calculated by Chi-Square of Ordinal by Ordinal to examine the trend of correlation between disease rates and length of use.

the length of using pacifiers was found for the reported symptom of allergic rhinitis (P value for trend = 0.025).

The relationship between the length of use of feeding bottles and the prevalence of disease was adjusted for all confounding factors shown in Table 4. Significant effects of using feeding bottles on children's wheezing/asthma (adjusted OR: 1.05, 95% CI 1.00–1.09), allergic rhinitis (adjusted OR: 1.04, 95% CI 1.00–1.08), and eczema (adjusted OR: 1.07, 95% CI 1.01–1.12) were found. The significant dose-dependent effects (P value for trend <0.05) between higher quartiles and the risk for having diseases or symptoms remained even after the adjustment for confounders was performed. Children who had used the feeding bottle until the time of this study (higher than the 75th percentile) were associated with a significant risk for reporting outcomes of interest compared to the first quartile (less than the 25th percentile) of subjects who had never used or stopped use before 2 years old.

4. Discussion

This study was the first to reveal that the use of feeding bottles among children might be one of the risk factors for the development of asthma and allergic diseases in Asian countries. Overall, we observed that a longer period of use of feeding bottles indicated a higher risk of diseases/symptoms among preschool children after adjustment for various confounders, including the children's age, gender, gestational age, birth weight, length of time being breastfed, the age first given infant formula or complementary foods, family history, parental educational levels, and smoking status, as well as the problem of indoor water damage.

Rising prevalence and morbidity of childhood asthma and allergic diseases has been observed globally [6, 7]. Taiwan has also been facing the same challenges during the past 20 years [8–10]. Previous studies have reported that about 80–90% of patients first succumb to allergic diseases before they are 5 years old [11]. However, none of the studies on this topic has investigated the prevalence of diseases among preschool-aged children in Taiwan. This study was the first to conduct a regional survey of children with an age range between 2 and 6 years old in order to explore the potential risk factors contributing to the development or presence of asthma and allergic diseases. From the current analysis, a prevalence of eczema was found to be the highest in children younger than 3 years old and to decrease gradually as age increased. On the contrary, the most prevalent period for allergic rhinitis was at 6 to 7 years old, while for diagnosed asthma, it was at 5 years of age. The current profile of prevalence for asthma and allergic morbidity corresponded to the theory of "atopic march," used for describing the phenomenon of the progression of allergic disorders among predisposed children. Eczema (atopic dermatitis) is thought to be an "entry point" for subsequent allergic diseases, including asthma and allergic rhinitis [12, 13].

The issue of plastic and health has attracted enormous attention in recent years [14], and there is also a possibility that any harmful chemicals emitted from pacifiers or feeding bottles could be the causal factor associated with this relationship. Only limited literature has reported relationships between childhood allergic diseases and the use of feeding bottles, pacifiers, or toys. One study from Japan indicated that the presence of asthmatic symptoms and eczema was associated with the use of latex for newborns who were less than 1 year old [15]. Another study conducted in Pakistan has shown early bottle feeding to be associated with higher total serum IgE levels in the study children [16]. Morass et al. in Austria also reported that children who had used pacifiers exhibited a higher percentage of wheezing symptoms during the previous 12 months [17]. The most interesting point is that a positive dose-dependent relationship was established by Morass et al. [17] between the frequency of boiling pacifiers and the percentage of children with wheezing or asthma. The authors tended to explain these phenomena through the "hygiene hypothesis," since boiling the pacifier less frequently might be a measure of generally lower hygiene levels, whereas boiling the pacifier daily might result in a decline in children's microbial exposure and, therefore, to increases risk of developing asthma and allergic diseases [17]. However, a study in China found that BPA was released within 24 hours from four brands of baby bottles at room temperatures of 24°C, 40°C, and 100°C, while increased temperatures led to higher release of BPA from the baby bottles [18]. Kubwabo et al. also showed the level of BPA from polycarbonate (PC) bottles increased with temperature and incubation time [19]. BPA has been concluded to might enhance allergic sensitization and bronchial inflammation during perinatal exposure and responsiveness in a susceptible animal model of asthma [20, 21]. A likely potential health risk of plastic exposure through the use of feeding bottles on asthma/allergies is therefore highly speculated. On the other hand, Sugita et al. [22] reported high levels of di-2-ethylhexyl phthalate (DEHP) (average 162 mg/g, 2.0–380 mg/g) in pacifiers and other related products that were used frequently by infants. Exposure to phthalates, one of most common plasticizers used in daily life, has shown its potential to be correlated with allergies and asthma in both animal and epidemiologic studies [2, 3]. Our recent publication also revealed that levels of indoor dust-borne benzylbutyl phthalate (BBzP) and dibutyl phthalate (DBP) as well as the urinary metabolites mono-n-butyl phthalate (MBP) and mono-2-ethylhexyl phthalate (MEHP) are associated with increased risks of allergies and asthma after taking into account exposure to other indoor pollutants [23].

We understand that the evidence might not be strong enough, constrained by the nature of a cross-sectional study design, and the casual relationship could not be established. However, it is also evident that such a study is aimed to raise new hypotheses between emergent exposures and the outcomes of significant interest. After further adjustments of confounders, it is believed that potential health concern of using feeding bottles should be attended to in the future.

5. Conclusions

While people have recently had dramatically increased exposure to various emerging chemicals in large amounts,

Table 4: The dose-effect relationship between disease prevalence and the age of stopping use of feeding bottles or pacifiers.

	Crude OR (95% CI)[†]	Adjusted OR (95% CI)[‡]	Quartile of using length for feeding bottles or pacifiers, adjusted OR (95% CI)[‡]				*P* values for trend*
			<25th (Ref.)	25th–50th	50th–75th	>75th	
Length of using feeding bottle							
Wheezing or asthma	**1.06 (1.03–1.10)**	**1.05 (1.00–1.09)**	1.00	1.10 (0.96–1.25)	1.11 (0.97–1.27)	**1.16 (1.01–1.32)**	**0.035**
Allergic rhinitis	**1.04 (1.00–1.07)**	**1.04 (1.00–1.08)**	1.00	1.09 (0.96–1.23)	1.01 (0.89–1.14)	**1.18 (1.03–1.34)**	**0.052**
Eczema	**1.09 (1.04–1.13)**	**1.07 (1.01–1.12)**	1.00	1.08 (0.91–1.28)	1.06 (0.89–1.25)	**1.25 (1.06–1.48)**	**0.017**
Length of using pacifiers							
Wheezing or asthma	**1.03 (1.00–1.07)**	1.02 (0.98–1.06)	1.00	1.11 (0.98–1.26)	1.08 (0.95–1.22)	1.07 (0.94–1.23)	0.370
Allergic rhinitis	**1.04 (1.00–1.07)**	1.02 (0.98–1.06)	1.00	1.08 (0.96–1.22)	1.11 (0.98–1.25)	1.04 (0.91–1.18)	0.441
Eczema	1.03 (0.99–1.08)	1.03 (0.98–1.09)	1.00	1.05 (0.90–1.23)	1.00 (0.85–1.17)	1.14 (0.96–1.35)	0.259

[†] Crude univariable effects were calculated by logistic regression.

[‡] ORs were calculated using multiple logistic regression with the adjustment of all factors tabulated in Table 1, including the persons completing the questionnaire, parental educational levels and smoking status, family history, child's gender, age, gestational age, birth weight, breastfeeding history, use of formula and complementary foods, food allergy status, and report of indoor water damage.

* *P* value for trend was calculated using the regression model while the predictor was considered as the continuous variable with the above-mentioned adjustment.

the group about which there is the most concern has been children, and the current study was the first to reveal the potential risk of using plastic consumer products, such as feeding bottles, as it was indicated from reported health status in an East Asian population. The specific underlying mechanism of feeding bottles usage resulting in the observed health outcomes warrants future investigation.

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Review Article

Sensitization to Cockroach Allergen: Immune Regulation and Genetic Determinants

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Asthma is a major public health concern. Cockroach allergen exposure and cockroach allergic sensitization could contribute to the higher prevalence of asthma. However, the underlying immune mechanism and the genetic etiology remain unclear. Recent advances have demonstrated that several receptors (PAR-2, TLRs, CLRs) and their pathways mediate antigen uptake from the environment and induce allergies by signaling T cells to activate an inappropriate immune response. Cockroach-derived protease can disturb airway epithelial integrity via PAR-2 and leads to an increased penetration of cockroach allergen, resulting in activation of innate immune cells (e.g., DCs) via binding to either TLRs or CLRs. The activated DCs can direct cells of the adaptive immune system to facilitate promotion of Th2 cell response and subsequently increase risk of sensitization. Mannose receptor (MR), as a CLR, has been shown to mediate Bla g2 (purified cockroach allergen) uptake by DCs and to determine allergen-induced T cell polarization. Additionally, genetic factors may play an important role in conferring the susceptibility to cockroach sensitization. Several genes have been associated with cockroach sensitization and related phenotypes (*HLA-D, TSLP, IL-12A, MBL2*). In this review, we have focused on studies on the cockroach allergen induced immunologic responses and genetic basis for cockroach sensitization.

1. Introduction

Asthma prevalence has markedly increased worldwide over the past three decades [1]. Exposure to indoor allergens is known to exacerbate asthma. Asthma symptoms due to exposure to cockroaches have been recognized since the 1940s. Scientific studies over the years have demonstrated that cockroach allergen is one of the major risk factors for the development of asthma [2–4]. Particularly, cockroach allergen exposure appears to have a greater effect on asthma morbidity than that of dust mite or pet allergen among inner-city children with asthma [5–7]. However, while there appears to be a rather clear relationship between allergen exposure and allergen sensitization or respiratory symptoms, the dose-response relationship is most relevant for "susceptible" individuals [7, 8]. Furthermore, a segment of the population, even when exposed to very high concentrations of allergen, will never become sensitized [9]. These studies suggested that there may be a genetic basis for allergen sensitization which contributes to the risk of asthma and/or the severity of asthma. It was recognized that interaction between gene and environment may control the development of asthma, but little is known regarding the causal relationship between cockroach exposure, sensitization, and asthma. A possible mechanism for the cockroach allergen induced allergic sensitization is illustrated in Figure 1. Cockroach allergen contains and produces many proteins and macromolecules, such as proteases [10, 11]. Cockroach-derived protease can disturb airway epithelial integrity and leads to an increased penetration of allergen proteins, resulting in activation of innate immune cells (e.g., dendritic cells (DCs)), which will direct cells of the adaptive immune system to Th2 cell development, lead to the lung inflammation and, subsequently, increased risk of sensitization [12, 13]. Protease-activated-receptor- (PAR-) 2, a receptor for protease, has been shown to mediate activation of airway epithelial cells [14, 15], and development of allergic diseases [16, 17]. Studies on PAR-2 deficient mice have demonstrated that PAR-2 mediates allergen-derived proteases in cockroach frass-induced airway allergic inflammation [18]. On the other hand, proteases may also serve as

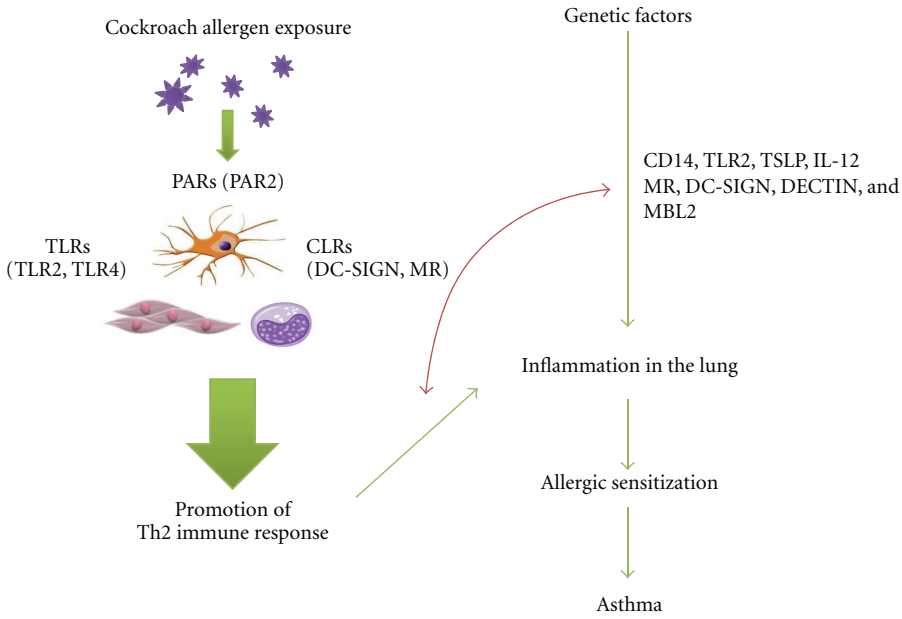

Figure 1: The mechanism of cockroach allergen-induced allergic sensitization. Cockroach-derived proteases can disturb airway epithelial integrity and lead to an increased penetration of cockroach allergen, which can activate innate immune cells (e.g., dendritic cells (DCs)) via binding to Toll-like receptors (TLRs) or C-type lectin receptors. The activated DCs can direct cells of the adaptive immune system to a promotion of Th2 cell response and subsequently increase risk of sensitization. On the other hand, genetic factors, particularly genetic variants in TLRs, CLRs, CD14, either alone or in interaction with cockroach exposure, confer the susceptibility to increased risk of cockroach sensitization and subsequently inflammation in the lung and asthma.

ligands for pattern recognition receptor (PPR). It was evident that German cockroach frass contains a Toll-like-receptor- (TLR) 2 ligand because it directly affected neutrophil cytokine production via TLR-2 [19, 20]. Furthermore, C-type lectin receptors (CLRs) are crucial in recognition of complex glycan structures and facilitate the endocytosis and presentation of pathogens [21–23]. Mannose receptor (MR), as a CLR, has been shown to mediate the uptake of diverse native allergens by DCs and to determine allergen-induced T-cell polarization [24, 25]. Significant binding of allergens and allergen extracts with variable binding activities to DC-SIGN and its receptor, L-SIGN, have been recently demonstrated [26]. Our recent studies have explored the mechanisms for cockroach allergen-induced allergic sensitization, including investigation of the Th1/Th2 cytokine profile of cocultured plasmacytoid dendritic cells (pDCs) and $CD4^+$ T-cells and identification of the "transcript signatures" for the immune response to cockroach allergen using high-throughput expression profiling of cocultured cells [27]. Furthermore, we performed initial genome-wide association studies (GWASs) for cockroach sensitization among African Americans. This paper focuses on studies on the cockroach allergen-induced immune response and genetic basis for cockroach sensitization.

2. Cockroach Allergen Exposure and Sensitization and Risk of Asthma

Indoor allergens associated with the development of asthma include those derived from cockroach [28], house-dust mites [29], animal dander [30], and mold spores [31]. Among them, cockroach allergen exposure is a strong risk factor for asthma associated with increased frequency and severity of childhood allergies and asthma among inner-city children [5, 6, 32]. For example, in the children's bedrooms, 50.2% had cockroach allergen levels that exceeded the disease-induction threshold, compared with 9.7% for dust mite allergen levels and 12.6% for cat allergen levels. The rate of hospitalization for asthma was 3.4 times higher among children who were skin test positive to cockroach antigen and whose bedrooms had high levels of cockroach allergen. The same group also had 78% more visits to health care providers, experienced significantly more wheezing, and missed more school because of asthma compared to the children who were skin test negative to cockroach allergen. Early life exposure to cockroach allergen can lead to allergic sensitization [1, 32], which also has been associated with an increased risk for persistent asthma and bronchial hyperresponsiveness and with a greater loss of function [33, 34]. Studies from the Inner-City Asthma Consortium showed that allergen-specific IgE levels were correlated with allergen exposure among sensitized participants ($P < 0.0001$ for cockroach), and specific IgE levels for cockroach are also correlated with a range of inflammatory, physiologic, and clinical markers, suggesting that the allergen-specific IgE level could be a surrogate measure of the combination of sensitization plus degree of exposure, and ultimately asthma severity [35]. Similarly, in the New York City Neighborhood Asthma and Allergy Study (NAAS), Chew et al. found that increased allergen exposure was associated with increased probability of sensitization (IgE) to cockroach ($P < 0.001$) [36], and cockroach allergen (Bla g2) was more prevalent in the bed

dust taken from the homes in the high asthma prevalence neighborhoods (HAPNs) compared with low asthma prevalence neighborhoods (LAPN), while sensitivity to cockroach allergen was twice as common at 23% versus 10% [7]. These studies further supported the notion that cockroach allergen exposure increases the risk of allergic sensitization, which is in turn related to the development of asthma. Importantly, it is worthwhile to note that the combination of cockroach sensitization and exposure to high levels of this allergen increased the frequency of asthma-related health problems overall in the inner city environment when compared with either of them alone, suggesting that allergic sensitization is a specific, major contributor to asthma morbidity for individuals with high exposure [5, 6].

3. Cockroach Allergen and Protease-Activated Receptors (PARs)

Environmental factors, including cockroach, house dust mite, and mouse, are thought to be risk factors for asthma. In particular, exposure to high levels of cockroach allergens in the home is a major risk factor for symptoms in sensitized individuals. Cockroach allergen is believed to derive from feces, saliva, and the bodies of these insects. Both *Blatella germanica* (German cockroach) and *Periplaneta Americana* (American cockroach) are important producers of major cockroach allergens [37]. German cockroach is especially ubiquitous, particularly in large, crowded cities in the United States [38]. However, it remains unclear how the cockroach allergens induce allergic sensitization and asthma. Cockroach allergen, like many of other allergens, HDM, fungi, pollen, and cat, contain and produce many proteins and macromolecules, such as proteases. Indeed, protease activities were detected in German cockroach frass and whole-body extract [10, 11]. It was suggested that cockroach-derived proteolytic enzymes disturb airway epithelial integrity, resulting in increased penetration of allergen proteins and increased risk of sensitization [12, 13]. Proteases may serve as ligands for PARs that mediate activation of airway epithelial cells and lead to the release of TNF, IL-8, and IL-6 [14, 15]. PAR-2, a major member in a family of proteolytically activated G-coupled receptors, has been associated with allergic diseases [16, 17]. Recent studies found that proteases from *A. alternata* act through PAR-2 to induce rapid increases in human airway epithelial [Ca2+]i *in vitro* and cell recruitment *in vivo, suggesting* critical early steps in the development of allergic asthma [39]. In addition, activation of PAR-2 was shown to increase the expression of thymic stromal lymphopoietin (TSLP), which activates DCs to polarize naive T-cells to Th2 cells [40]. Further studies on PAR-2 deficient mice have demonstrated that PAR-2 mediates allergen-derived proteases in cockroach frass-induced airway allergic inflammation, including increased airway hyperresponsiveness, Th2/Th17 cytokine release, serum IgE levels, cellular infiltration, and mucin production, but the effect was only observed when allergen was administered through the mucosa [18]. Collectively, these data suggest that proteases may link the innate and adaptive immune responses via PAR-2. In contrast, proteases may also serve as ligands for pattern recognition receptor (PPR). It was evident that German cockroach frass contains a TLR2 ligand, which actives neutrophils [19] and leads to release of MMP-9 and decreased allergic responses to cockroach frass [20]. However, it still remains uncertain about the presence and activities of proteases in cockroach extract, because neither serine protease inhibitor nor cysteine protease inhibitor can inhibit PAR-2 cleavage by cockroach extracts [41]. This was consistent with the studies on one of the purified cockroach allergens, Bla g2. Bla g2 has been shown to be a major antigen according to the investigation of IgE-mediated response (60%). Although Bla g2 shares sequence homology with the aspartic proteinase family of proteolytic enzymes, it lacks proteolytic activity in a standard milk-clotting assay using casein as a substrate [42].These findings suggest that it may be enzymatically inactive factors, other than enzymatic activity, which play a role in cockroach-induced immunological response.

4. The Immunological Role of Dendritic Cells (DCs) in Shaping the Immune Response

DCs are the most powerful antigen-presenting cells (APCs) that process cockroach antigen and play a critical role in the initiation of the immune response and T-cell polarization [43–45]. Animal models have suggested that DCs are vital for both initiation and maintenance of allergic airway inflammation in asthma [46]. There are two major subsets of immature DCs that circulate in blood, namely, the $CD11c^{+}$, $CD123^{low}$ myeloid DCs (mDCs), and $CD11c^{-}$, $CD123^{high}$ plasmacytoid DC (pDCs). There is accumulating evidence from animal models that mDCs have a crucial role in the development of allergic asthma [47, 48]. In particular, Mo et al. found an increased airway hyperresponsiveness, eosinophil counts, and Th2 cytokines in BAL after intratracheal administration of OVA-pulsed mDCs [49]. In contrast, pDCs have been reported to inhibit allergic airway inflammation and Th2-type cytokine production in a mouse model of asthma [19], or play a limited role in priming T-cells in the mouse model of asthma [49]. It seemed that the interaction between pDCs and mDCs might control Th1/Th2 balance with a proallergic role for mDCs and antiallergic properties of pDCs. However, human pDCs can also stimulate allergen-dependent T-cell proliferation and Th2-type cytokine production as efficiently as mDCs [50]. In patients with atopic rhinitis, dermatitis, and asthma, there is a strong local increase in pDCs after allergen challenge [51–54]. It is possible that both pDCs and mDCs triggering either Th1-type or a Th2-type immune response may depend on the local microenvironment and stimulus. This was supported by our recent studies demonstrating that cocultured pDCs and $CD4^{+}$ T cells produce significantly elevated levels of IL-13, IL-10, and TNF-α, but undetectable levels of IL-12p70, upon exposure to cockroach extract [27]. Furthermore, the increased levels of IL-13 were found in cells from cockroach allergic subjects when compared with cockroach nonallergic individuals. To identify the major players in the DC-mediated initiation of the immune

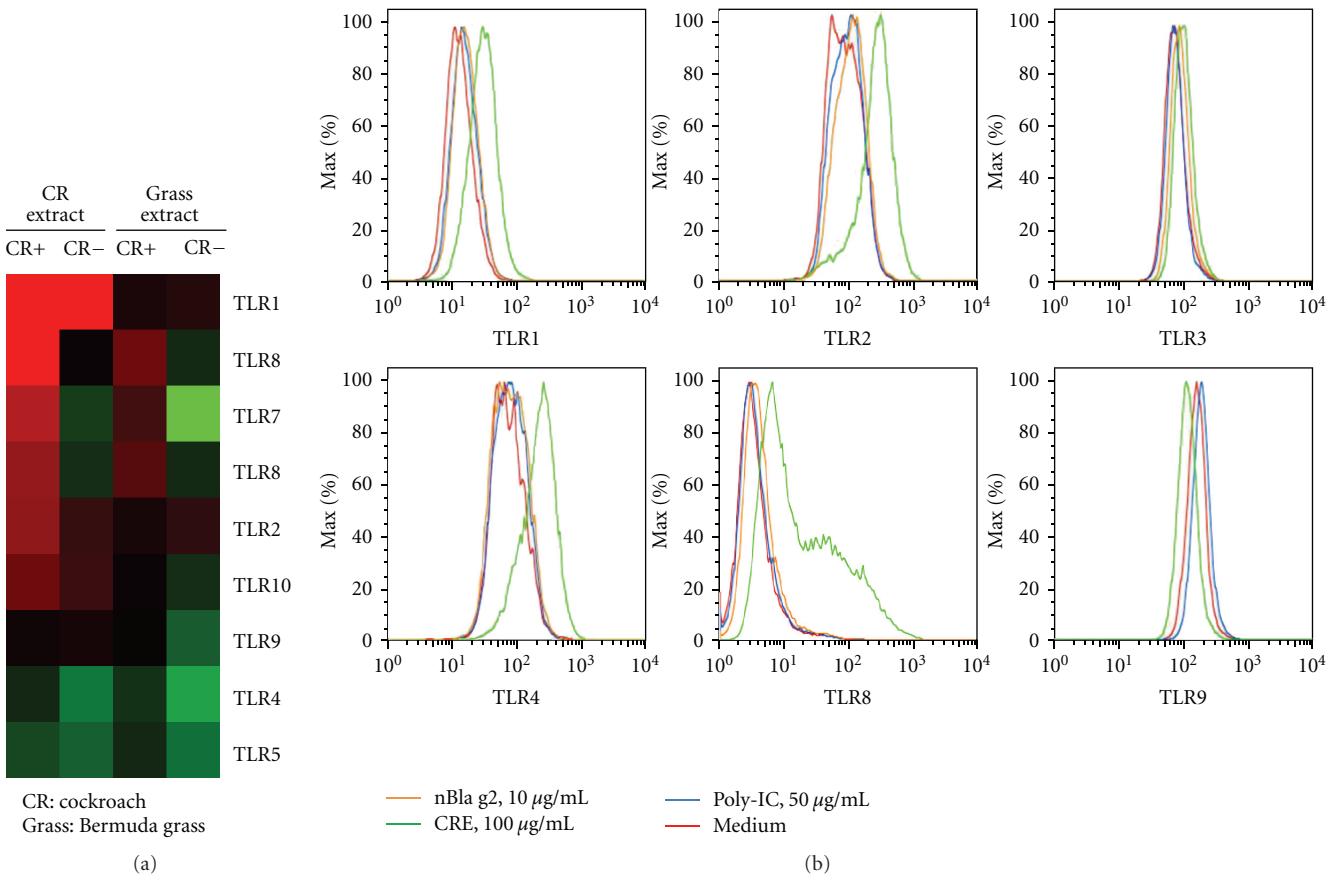

Figure 2: *TLR* gene expression in cocultured pDCs and CD4$^+$ T cells and human THP-1 cells. (a) Microarray analysis of TLR transcripts expressed in cockroach allergen (CR) and Bermuda grass allergens treated cocultured pDCs and CD4$^+$ T cells from cockroach-sensitized and -nonsensitized subjects. Upregulated genes are represented in red and downregulated genes in green. (b) TLR expression in THP-1 cells was detected at the protein levels by FACS (red, medium; orange: nBla g2; green: CRE, 100 ug/mL; blue: Poly-IC, 50 ug/mL).

response and T-cell polarization allergic disease, we performed gene array analyses (24000 transcripts and variants) in cocultured pDCs and CD4$^+$ T cells aimed at identifying the "transcript signature" responsible for the initiation of the immune response and T-cell polarization. We found more than 50 genes uniquely expressed in cockroach treated cells, including *CD14*, *S100A8*, *CCL8*, IRF7, and *IFI44L*. Among these, *CD14* is one of the most replicated genes associated with asthma and associated traits [55]. A functional polymorphism in the promoter of *CD14* has been shown to modulate specific responses to environmental aeroallergens, at least among individuals predisposed to atopy [56]. Most importantly, pathway analysis suggested that both IFN and TLR signaling pathways are two major pathways in cockroach allergen-induced immunological responses. It is well known that TLRs, transmembrane proteins, highly expressed in DCs, play an important role in mediating allergen-induced innate and adaptive immune response [53]. Exogenous antigen presentation by DCs in the absence of direct TLR stimulation generally leads to tolerance [57]. Moreover, efficient generation of effector T-cell responses by DCs is dependent on the presence of TLR ligands in the phagosome containing the antigen being presented [58], suggesting that TLR signaling is critical in mediating antigen-induced adaptive immune response. It is likely that cockroach allergens interact with DCs via TLRs and lead to DC maturation, cytokine production, and APC function in T-cell polarization. Among all the TLR genes in our initial gene array analysis, TLR2, TLR3, TLR7, and TLR8 were upregulated in the cockroach allergic group compared with cockroach nonallergic group (Figure 2(a)). Of these, increased TLR2 and TLR8 were also validated at the protein levels (Figure 2(b)), suggesting that TLR2 and TLR8 may be important TLRs for cockroach sensitization. Indeed, recent report has provided strong evidence that TLR2 and TLR8 may confer susceptibility to asthma and related atopic disorders [19, 59]. In particular, German cockroach contains a TLR2 agonist and directly activates cells of the innate immune system, which may be critical in linking innate and adaptive immunity [19]. Genetic variation in TLR2 (rs4696480) has been identified as a major determinant of the susceptibility to asthma and allergies in children of farmers.

C-type lectin receptors (CLRs), on the other hand, are crucial in recognition of complex glycan structures on various pathogens and have evolved to facilitate the endocytosis and presentation of pathogens [21–23]. In fact, signaling through CLRs has been shown to be able to induce T-cell

activation and tolerance and modify the cellular response via cross-regulation of the TLR-mediated effect [23]. These regulatory functions have been clearly exemplified by three members of the CLRs, DC-SIGN (dendritic cell-specific, CD209), L-SIGN (CD299), and MR [60, 61]. Thus, distinct DC subsets with different sets of CLRs may recognize distinct classes of antigens to induce tolerance or activate immunity, wherein complex glycan structures on antigens may play a key role. While the direct interaction between allergens and CLRs has not been demonstrated, the mere fact that most allergens contain complex glycan structures raises the possibility that allergen-CLR signaling may modulate DCs and subsequent immune response. Indeed, MR has been shown to mediate the uptake of diverse native allergens by DCs and determines allergen-induced T-cell polarization through modulation of indoleamine 2,3 dioxygenase (IDO) activity [24]. In addition, Emara et al. showed that Fel d 1 interacts with immune cells by MR, and found that MR probably plays a pivotal role in allergic response to Fel d 1 [25]. Study on peanut allergens has provided a suggestive evidence that one of the major allergens, Ara h1, is able to polarize Th2 response via its likely interaction with DC-SIGN on monocyte-derived DCs [62]. We also found that mDCs produced a large amount of IL-10 after treatment with German cockroach extract, and that the increased expression was blocked by anti-DC-SIGN (Figure 3), suggesting that DC-SIGN in mDCs mediates cockroach allergen-induced allergic response. Hsu et al. demonstrated significant binding of allergens and allergen extracts with variable binding activities to DC-SIGN and its receptor, L-SIGN [26]. These allergens include bovine serum albumin (BSA) coupled with a common glyco-form of allergens and a panel of purified allergens (BG60 from Bermuda grass pollen, Der p2 from house dust mite). Interaction between BG60 and DC-SIGN-activated Raf-1 and ERK kinases and led to the induction of TNF-α expression. These studies identified an important signaling pathway for allergen-induced immunity, and, importantly, they suggested that there may be a cross-regulation between CLRs, TLRs, and PAR2.

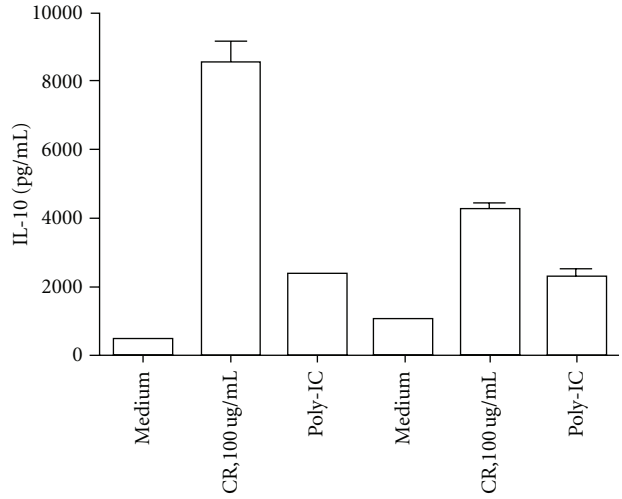

Figure 3: Cockroach allergen induced-IL-10 secretion in mDCs. IL-10 production was detected in the cockroach-extract- (CR-) treated alone (100 ug/mL) or together with anti-DC-SIGN mDCs. IL-10 levels were measured by ELISA.

5. Genetic Basis for Cockroach Sensitization

While there appears to be a rather clear relationship between allergen exposure and allergen sensitization, the dose-response relationship is most relevant for "susceptible" individuals [1, 8]. Conversely, the majority of individuals, when exposed to very high concentrations of allergen, never become sensitized [9]. Indeed, one of our previous studies has implied a role for genetic susceptibility wherein cockroach sensitization was found to be more prevalent among African Americans compared with European Americans living in the Baltimore-Washington, DC, metropolitan area, even after controlling for socioeconomic status [63] These findings suggest that cockroach sensitization is not a function of cockroach allergen exposure alone, and that genetic susceptibility may be important. Indeed, significant familial aggregation of allergic sensitization to cockroach allergen has been observed in the Chinese population [64]. In a genome-wide linkage study of asthma-related phenotypes on 2,551 individuals from 533 families, Xu et al. provided suggestive evidence of linkage at D4S1647 for skin reactivity to cockroach defined by skin prick tests (SPTs) (pointwise $P = 0.0003$) [65]. Hunninghake et al. recently reported significant evidence of linkage to cockroach-specific IgE on chromosome 5q23 (peak LOD, 4.14 at 127 cM) [66]. Within this genomic region, there is a compelling candidate gene with experimental evidence of female-specific effects on lung disease, thymic stromal lymphopoietin (TSLP). In a sex-stratified analysis, the T allele of single-nucleotide polymorphism (SNP) rs2289276 in the 5'untranslated region of *TSLP* was associated with reductions in IgE concentrations to cockroach. Interestingly, the same *TSLP* SNP rs2289276 also showed significant association with lower levels of total IgE (tIgE,$P = 6.24 \times 10^{-6}$) in our initial analyses of GWAS for tigE among cockroach allergic individuals. In a study on *HLA-D* associations and cockroach sensitization, Donfack et al. [67] observed associations with alleles of the *HLA-DR* molecule, *DRB1*0101* in Hutterites and *DRB1*0102* in African Americans, and hypothesized that the *DRB1*0102* allele may have a higher affinity for cockroach allergens and elicit a stronger response to bind antigens than *DRB1*0101* allele. Leung et al. observed that polymorphisms in the *Mannose-binding lectin* (*MBL*) gene may protect against cockroach sensitization in Chinese children [68], and Pistiner et al. demonstrated that polymorphisms in *IL12A* were associated with cockroach sensitization among children with asthma in both Costa Rica and European-ancestry children with asthma in the Childhood Asthma Management Program (CAMP) [69]. We performed a genome-wide association analysis for cockroach sensitization in the African American population. A summary of the results is shown for a trend in the association between cockroach sensitization and each SNP measured in the GWAS (Figure 4). Overall, there were 7,768 SNPs in 4,018 genes with P value < 0.01. When specifically limiting the SNPs to those at $P < 0.001$, we

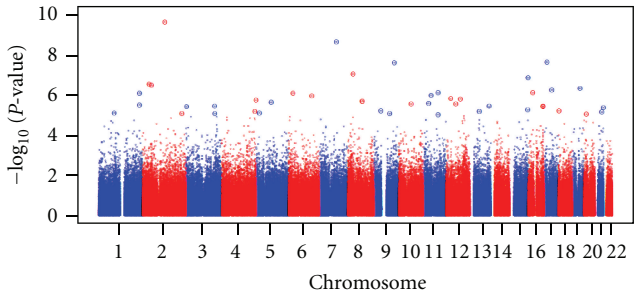

FIGURE 4: Overview of genome-wide association study of cockroach sensitization in the African American population. Manhattan plot showing the association of 644,709 SNPs by chromosome for cockroach allergy versus $-\log_{10}P$ value. The x-axis represents genomic position, and the y-axis shows $-\log_{10}(P)$.

found at least 12 genes that had differentially gene expression in our gene array analysis for cockroach allergen exposure (*IFI44, CTLA4, LYN, BCL6, CCL1, MERCK, HERC6, TRIB1, DNAPTP6, SAMSN1, RAFTLIN*, and *GMZB*). Among those, *CTLA4* [70], *BCL6* [71], *GZMB* [72], and *CCL1* [73] have been associated with allergy and asthma and related phenotypes. The results suggested that integrating GWAS with gene expression profiling studies will be useful approach to identify candidate for cockroach allergic sensitization.

6. Conclusion

Asthma is a major public health concern. Cockroach allergen exposure and cockroach allergic sensitization could contribute to the higher prevalence of asthma. Although studies on the causal relationship between cockroach allergen exposure, sensitization, and asthma are very limited, several receptors (*PAR-2, TLRs, CLRs*) and their pathways have been seen to be important in mediating antigen uptake from the environment and inducing allergies by signaling T-cells to activate an inappropriate immune response. In particular, cockroach-derived protease can disturb airway epithelial integrity via PAR-2 and leads to an increased penetration of cockroach allergen, resulting in activation of innate immune cells (e.g., DCs) via binding to either *TLRs* or *CLRs*. The activated DCs can direct cells of the adaptive immune system to facilitate promotion of Th2 cell response and subsequently increase risk of sensitization. However, it remains largely unknown whether different cell types expressing different sets of receptors may recognize distinct classes of cockroach allergens to induce different immune responses, and whether these receptors have a cross-regulation. On the other hand, genetic factors, particularly genetic variants in *TSLP, MBL2, CD14*, and *IL-12A* have been associated with cockroach sensitization and related phenotypes. It would be of interest to study whether these genes in interaction with cockroach exposure confer an increased susceptibility to the risk of cockroach sensitization when compared with these genes analyzed alone. Continuous studies, we believe, on cockroach allergen-induced innate immunity and gene-environment interaction will add value to the existing research investment in these studies and offer novel insight into the molecular mechanisms that cause cockroach sensitization and subsequently asthma.

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Review Article

Different Implications of Paternal and Maternal Atopy for Perinatal IgE Production and Asthma Development

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Asthma is a hereditary disease associated with IgE-mediated reaction. Whether maternal atopy and paternal atopy have different impacts on perinatal IgE production and asthma development remains unclear. This paper reviews and summarizes the effects of maternal and paternal atopy on the developmental aspects of IgE production and asthma. Maternal atopy affects both pre- and postnatal IgE production, whereas paternal atopy mainly affects the latter. Maternally transmitted genes *GSTP1* and *FceRI-beta* are associated with lung function and allergic sensitization, respectively. In IgE production and asthma development, the maternal influence on gene-environment interaction is greater than paternal influence. Maternal, paternal, and/or postnatal environmental modulation of allergic responses have been linked to epigenetic mechanisms, which may be good targets for early prevention of asthma.

1. Introduction

The prevalence of asthma has dramatically increased over the past few decades, particularly in children [1]. Most childhood allergic diseases, such as atopic dermatitis and asthma, develop in the first few years of life [2, 3]. Understanding the developmental process of allergic diseases, which have long been attributed to IgE-mediated mechanisms [4, 5] and identifying factors that play important roles in perinatal IgE production and asthma development may help early predict and prevent the occurrence of allergic diseases. Evidence has shown that allergy sensitization may occur in fetal life [6, 7], and a number of factors have been shown to affect the development of allergic disease; family history of atopy, environmental exposure in urban areas, maternal nutritional status and stress during pregnancy, and the time and method of complementary food initiation are all potential factors that contribute to asthma. In addition, genetic polymorphisms originating in maternal or paternal inheritance have been implicated in IgE production and asthma development. This paper reviews and addresses the difference between paternal and maternal inheritance and environment in IgE production and asthma development.

2. Association of Antenatal IgE Production with Asthma

An increase in blood IgE levels has long been implicated in the development and severity of asthma [8, 9]. IgE production and allergy sensitization are both active processes in the prenatal and perinatal periods and are potentially influenced by genetic factors and the intrauterine and postnatal environments. Antenatal allergy sensitization with IgE production, reflected by the elevation of cord blood serum IgE (CBIgE), has been studied as a predictor of asthma and other IgE-mediated allergic diseases; however, the results are controversial (Table 1). Some studies indicate that higher CBIgE levels correlate with the development of aeroallergen sensitization [10–12], recurrent wheezing in childhood [13],

Table 1: Does CBIgE elevation predict allergy?

Parameters	Population studied, country	Reference
Parameters correlated with elevated CBIgE		
Skin-prick test at age 4 yr	1456, England	[10]
Allergic sensitization and recurrent wheezing at age 7 yr	380 high-risk newborns, Canada	[13]
Allergic sensitization at 4 and 10 yr and asthma at 10 yr	1456, USA	[14]
Skin-prick test at age 5 yr, allergic rhinoconjunctivitis at age 20 yr, and total IgE at ages 11 and 20 yr	200, Finland	[15]
High IgE and allergic sensitization between the ages of 18 and 24 months	1884, Sweden	[11]
Total IgE and allergic diseases before 5 years of age	1884, USA	[12]
Parameters not correlated with elevated CBIgE		
No significant association with recurrent wheezing	1314, Germany	[16]
Not better than family history to predict infant atopy	2814, USA	[17]
Family history of atopy far more sensitive than CBIgE	1111, UK	[18]

later development of childhood asthma [14], and allergic rhinoconjunctivitis in adulthood [15]. However, other studies yielded discouraging results indicating that CBIgE elevation lacks the sensitivity for predicting the development of allergic diseases in childhood [16–18]. The inconsistencies may be due to differences in ethics, cut-off values of CBIgE levels, and definitions of allergic diseases in these cohorts. However, a recent study found strong evidence that maternal-fetal transfer may be a common cause of increased CBIgE levels, especially in newborns with elevated cord blood IgA levels [19] or allergen-specific IgE [20], which is not commonly found in the cord blood of newborns, suggesting maternal-fetal transfer of IgE or contamination of maternal blood. As shown in Table 1, several studies have shown a correlation between elevated CBIgE levels and allergic sensitization and/or asthma, whereas other studies revealed no correlation [10–18].

To determine whether prenatal IgE production reflects CBIgE elevation and the development of allergic diseases, we followed up a birth cohort of 230 newborns from the prenatal stage to 6 months, 18 months, 3 years, and 6 years of age. With CBIgE levels ≥0.5 kU/L considered elevated, our preliminary analysis of the total IgE levels in the 230 newborns who completed the followup revealed that newborns with elevated CBIgE (0.5 kU/L) exhibited a significantly higher risk of atopic dermatitis (odds ratio (OR), 2.067; 95% confidence interval (CI), 1.392–3.071) and allergic rhinitis (OR, 1.840; 95% CI, 1.212–2.791), but not asthma, at 6 years of age. The sensitivity and specificity of elevated CBIgE (0.5 kU/L) for predicting atopic dermatitis and allergic rhinitis were 28.5% and 83.8% and 23.9% and 85.3%, respectively. Elevated CBIgE (0.5 kU/L) was also highly correlated with elevated IgE levels at 6 years of age (150 kU/L) (OR, 2.671; 95% CI, 1.424–5.010); however, it exhibited poor sensitivity (35%) but high specificity (83.2%). This indicates that CBIgE levels are related to the development of allergic diseases and that the CBIgE prediction of allergic outcomes during childhood may be specific but not sensitive enough for clinical application. Other factors, such as elevated umbilical cord blood CCL17 levels [21], CCL22 levels [22], or reduced IFN-γ levels with enhanced IL-4-producing CD4+ cord blood T cells [23], have been shown to be associated with atopic dermatitis in infancy. Cord blood 25-hydroxyvitamin D levels are inversely associated with the risk of childhood wheezing [24]. More studies on the CBIgE levels and/or other chemokine or cytokine levels of cord blood are needed to improve their prediction value for childhood allergic diseases.

3. Different Implications of Paternal and Maternal Atopy for IgE Production and Asthma

The effect of maternal total IgE levels or atopy on cord blood IgE levels has been well recognized [25–30]; on the other hand, paternal total IgE levels and paternal atopy have little effect on antenatal IgE production or early atopy [25–29]. However, paternal total IgE level, like maternal total IgE levels, highly correlate with total IgE levels in children of preschool age [31]. In other words, maternal total IgE levels or sensitization may positively correlate with antenatal and postnatal IgE production; however, paternal total IgE levels or sensitization has little effect on antenatal IgE production but has a significant impact on the IgE production at preschool age (around 4–6 years). However, some studies have shown a poor association between parental atopy and atopic dermatitis in children up to 4 years of age [32, 33]. Although both maternal and paternal histories of asthma are associated with childhood asthma, various studies have shown that maternal history of asthma or atopy is one of the most important risk factors for childhood asthma [34–37] and is associated with increasing risk of admission for childhood asthma [38]. A 2-stage case-control study in Canada revealed that children born to asthmatic mothers are at a higher risk of developing asthma than children born to nonasthmatic mothers are (32.6% and 14.1%, resp.) [39]. Furthermore, paternal asthma is a significant and strong predictor of asthma or airway hyperresponsiveness in school-age

Table 2: Effect of parental background on IgE production and asthma development.

	Maternal background	Paternal background
Gene	Maternal antioxidant gene polymorphisms: GSTP1 [51] GSTM1 and GSTT1 [52] Polymorphism of the beta-chain of high-affinity IgE receptor (FceRI-beta) [53], and 11q13 allele [54]	An allele at chromosome 7p [50]
Environment	Maternal asthma [34–39] Fetal exposure to tobacco smoke, household allergens, and latex and/or biocides [58–63, 65] Fetal exposure to traffic air pollution [64] Maternal prenatal exposure to farm, farm animals, and cat or dog [58, 66, 68] Mediterranean diet, fish intake, fatty acid status, and folic acid supplements during pregnancy [24, 69, 72, 73]	Paternal asthma [40–43] Paternal occupational flour dust exposure [65]

children [40–42]. In a study on asthma in consanguineous families, paternal asthma increased the risk of asthma in both boys and girls ($P = 0.021$ for boys, $P < 0.001$ for girls), whereas maternal asthma had no significant impact on asthma in the offspring [43]. These results indicate that the effect of maternal atopy on IgE production and allergic diseases of the offspring begins at the fetal stage and continues to infancy and childhood; however, the impact of paternal atopy is not apparent until childhood.

Accumulated evidence has also shown that maternal asthma history has a greater impact on the subsequent development of allergic asthma in the offspring than paternal asthma history has. In a meta-analysis of 33 studies from 1966 to 2009 investigating the impact of maternal asthma and paternal asthma on the asthma of their offspring, the OR for asthma in children of asthmatic mothers was significantly higher than that in children of nonasthmatic mothers (3.04; 95% CI, 2.59–3.56). The corresponding OR for asthma in children of asthmatic fathers only increased to 2.44 (2.14–2.79). When comparing the OR, maternal asthma conferred a greater risk of the disease than paternal asthma did (3.04 versus 2.44, $P = 0.037$) [44]. However, some studies have shown that maternal and paternal airway hyperresponsiveness (AHR) or asthma increases the risk of AHR or asthma in their offspring [45, 46]. The opposite was observed by Kurzius-Spencer and colleagues, who showed a strong father-offspring (particularly father-son), but not mother-offspring, correlation in airway responsiveness among children [47]. Dold and colleagues have also shown that paternal asthma history has a much greater impact, with a relative risk of 4.4, than maternal asthma history has, with a 1.5-fold risk of the occurrence of wheezy bronchitis in children between the ages of 9 and 11 [48]. Similarly, in a study of 1,041 asthmatic children, Raby and his colleagues found that children with a paternal history of asthma, but not with a maternal history of asthma, showed significantly greater AHR than those without such history did [49]. Another study by Litonjua and colleagues [37] also showed that paternal contributions to the risk of childhood asthma have a greater influence on older children. These results suggest that AHR and asthma are independently inherited. Paternally derived and maternally derived asthma modulate different gene expression pathways or epigenetic mechanisms to transmit different phenotypes (AHR and asthma) in the offspring.

In our birth cohort study, we analyzed whether the presence of paternal or maternal atopy, as defined by total IgE > 150 kU/L [26], influenced IgE production from the newborn stage to 6 months, 18 months, 3 years, and 6 years of age. As shown in Figure 1, maternal atopy, but not paternal atopy, significantly affected antenatal IgE production, as reflected by CBIgE elevation (Figures 1(a) and 1(c)). Maternal atopy was significantly associated with the log-transformed IgE levels at 6 months, 18 months, 3 years, and 6 years of age, whereas paternal atopy was only significantly correlated with log-transformed IgE levels at 3 years and 6 years of age (Figures 1(b) and 1(d)). These results strongly indicate that maternal influence on IgE production is exerted from the antenatal stage through childhood, whereas paternal influence on IgE production begins from early childhood and increases with increasing age.

4. Effects of Paternal and Maternal Inheritance and Environment on IgE Production and Asthma

Advances in the identification of asthma-susceptibility genes may provide some insights into the molecular mechanisms underlying maternal and paternal influence on childhood asthma. As shown in Table 2, Leaves and colleagues showed that a region of chromosome 7p, restricted to siblings sharing alleles inherited from fathers, not from mothers, is tightly linked with AHR in an Australian population, suggesting paternally derived alleles at this locus might affect airway responsiveness [50]. Maternal antioxidant gene polymorphisms (*GSTP1* and *GSTM1*, *GSTT1*) have been regarded as specific risk factors for asthma in the offspring and may modify the relationship between prenatal acetaminophen exposure and childhood asthma [51, 52]. Traherne and colleagues have shown that the polymorphism of the *high-affinity IgE receptor beta-chain* (*FceRI-beta*) has a strong association with positive allergy skin-prick tests and greater allergen-specific IgE levels when these polymorphisms are inherited from the mothers [53]. Cookson and his colleagues found that the transmission of atopy at the chromosome 11q13 allele is

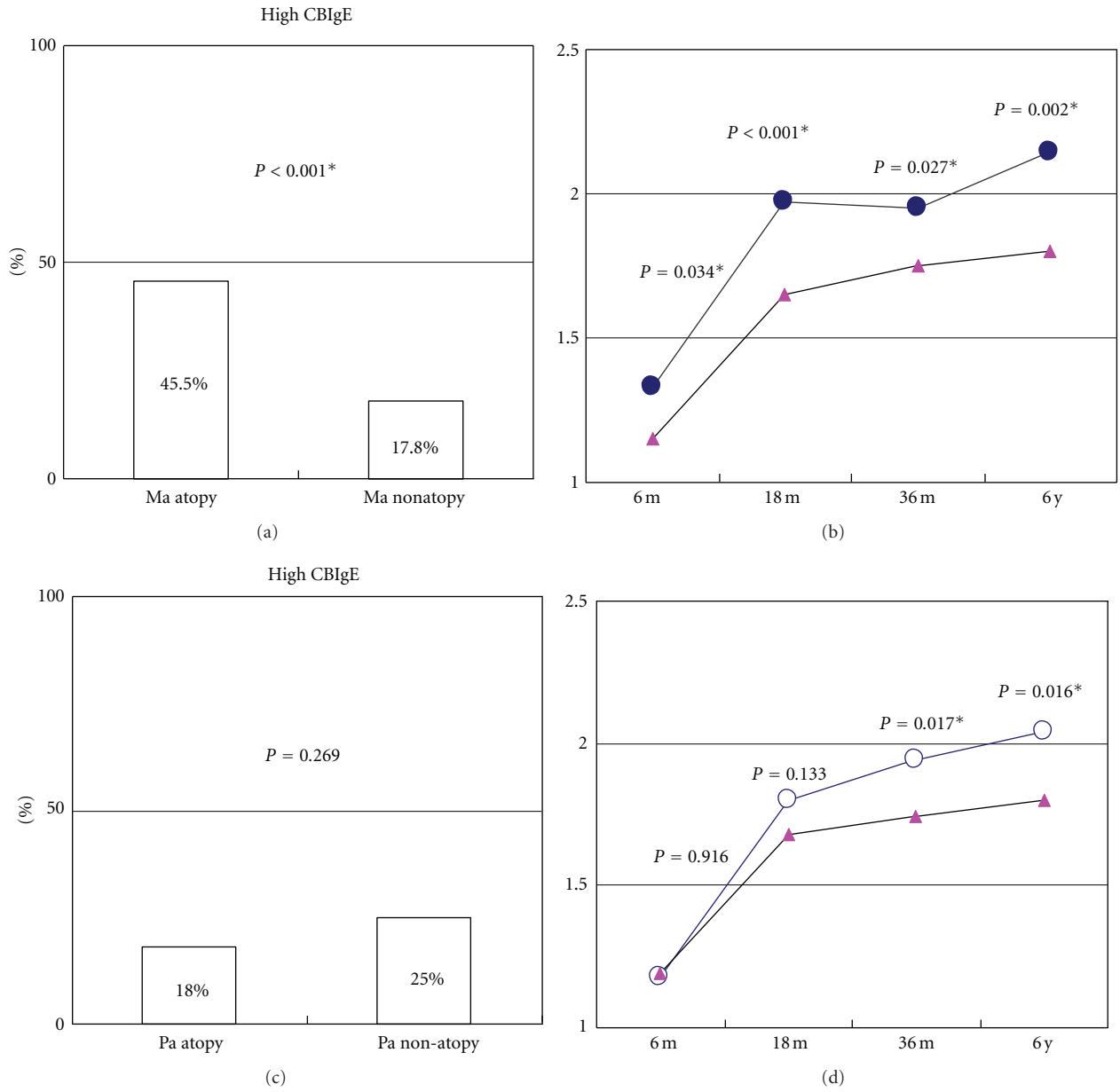

Figure 1: Different implications of maternal and paternal IgE levels for antenatal IgE level and postnatal IgE production at different ages in our cohort study. (a), (c): Maternal (Ma) atopy, defined as IgE > 150 kU/L, but not paternal (Pa) atopy, significantly affected antenatal IgE production, reflected by CBIgE elevation (>0.5 kU/L). (b), (d): Maternal atopy (solid circles) was significantly associated with log-transformed IgE levels at 6 months (6 m), 18 months (18 m), 3 years (36 m), and 6 years (6 y) of age, whereas paternal atopy (open circles) was only significantly associated with log-transformed levels at 3 and 6 years of age.

detectable only through the maternal line [54]. These parent-derived alleles associated with IgE production and asthma provide insights into the impact of gender on the inheritance of IgE production and the development of asthma.

There are several possible reasons to explain why mothers and fathers have different impacts on IgE production and asthma development in their offspring, including exclusive exposure to maternal environmental factors during fetal development, fetomaternal-shared perinatal environmental exposures (including breastfeeding), different hormones, and distinct genetic imprinting [49]. Moreover, certain genetic alleles may have sex-specific effects and may be expressed to a greater level in male or female individuals, thereby making more specific contributions when inherited from the mother or father.

Besides inheritance, maternal and paternal environment can affect the development of asthma differently. Several lines of evidence have indicated that factors present during fetal development influence immune responses and allergen sensitization in early life. During pregnancy, the fetomaternal interface is surrounded by Th2-prone environment [55], which may suppress fetus-directed maternal Th1 immune

responses [56]. This Th2 environment may be a good niche for fetal allergy sensitization, because the Th2 cytokine microenvironment may prime T cells toward allergic differentiation [57]. Maternal environmental factors, including maternal prenatal exposure to tobacco smoke [58–62], household allergens [63], traffic air pollution [64], and maternal occupational exposure to latex and biocides [65], are associated with childhood asthma; however, increasing maternal age, maternal prenatal exposure to cat or dog [58, 66], maternal fish intake [67], and maternal exposure to farming environments [68] have been shown to exert protective effects. One study revealed that folic acid supplements during pregnancy are associated with a slightly increased risk of wheezing and lower respiratory tract infections up to 18 months of age and suggests that methyl-group donors in the maternal diet during pregnancy influence respiratory health in children via epigenetic mechanisms [69]. Another study showed that serum folate levels are inversely associated with total IgE levels and that a dose-response relationship exists between serum folate and outcomes of high total IgE level, atopy, and wheezing [70]. However, a recent study does not support the relationship between folic acid supplement and asthma development [71]. In contrast, fewer paternal environmental factors are associated with IgE production and asthma development. It has been shown that paternal occupational flour dust exposure was associated with the development of asthma [65]. These results indicate that environmental factors during pregnancy, directly or indirectly, play important roles in allergic sensitization or disease development.

Environmental factors may influence gene expression, cytokine secretion, T-cell differentiation, and the development of allergic diseases via epigenetic mechanisms, possibly by DNA methylation and histone modification. In a study using the *Aspergillus fumigatus* allergen murine model, chronic inhalation of diesel exhaust particles induced hypermethylation at the CpG-45, CpG-53, and CpG-205 sites of the *IFN-γ* promoter in CD4 cells, and hypomethylation at CpG-408 in the proximal *IL-4* promoter in CD4 cells, both of which significantly correlated with higher IgE production [74]. Perera and colleagues found that transplacental exposure to traffic-related polycyclic aromatic hydrocarbons (PAHs) is significantly associated with hypermethylation of *acyl-CoA synthetase long-chain family member 3* (*ACSL3*) [75], which may diminish fatty acid utilization and possibly influence membrane phospholipid composition. Whether these functional changes directly affect the development of the asthmatic phenotype is unknown and deserves further investigation.

5. Paternal and Maternal Influence on Gene-Environment Interactions in Perinatal IgE Production and Childhood Asthma

IgE is produced by activated B cells, which interact with Th2 cells and undergo isotype class switching after the induction of Th2 cell-derived cytokines, particularly *IL-4* and *IL-13*. Some lines of evidence indicate that IgE production in children and adults is under strong genetic control [76, 77], with heritability ranging from 60% to 87% in childhood. We previously found that 21 SNPs in 14 allergy candidate genes on chromosomes 4, 5, 6, 9, 10, 11, 12, 16, and 20 are associated with elevated levels of CBIgE [78], a finding similar to findings of the studies on genetic association of serum IgE and asthma [79, 80].

We have also previously shown the effects of gene-gene (IL13, rs20541 interaction between *CCL17*, rs223900, and *CXCL10*, rs867562 on antenatal IgE production) and gene-environment (maternal atopy alone and its interaction with *PIM1, GPIAP1, NOS2A, CTLA4, ADAM33, LTA, PDE2A, GSR, IL13, FGF, CCL22,* or *CAT* can affect antenatal IgE production) interactions on CBIgE production [78]. Another study in Australia made a similar observation that genetic variants in the Th2 pathways, particularly in the *IL-13, IL-13RA1,* and *STAT6* genes, are significantly associated with CBIgE concentration individually and jointly. The gene-gene interaction and ethnic heterogeneity observed in that study are similar to those observed in our study [93]. Both studies indicate that genetic regulation of IgE production begins in the prenatal stage and is influenced by different genetic backgrounds and maternal atopy status via gene-environment interactions.

In IgE production and asthma, the maternal influence on gene-environment interaction is more prominent than the paternal influence is. Several studies have supported the gender-dependent gene-environment interactions on asthma development, such as polymorphisms of *CTLA-4* [26], *GSTM1* [94, 95], *GSTP1* [96], *IL-13* [97], *IL-1Ra* [98], *βAR* [99], *TGF-beta1* [100], *HLA-G* [101, 102], *CD14* [103–106], and *TLR2* [107], may influence the development of asthma through interactions with other maternal environmental factors, such as maternal tobacco smoke exposure, maternal atopy, or maternal prenatal exposure to a farming environment. Sensitization of the fetus due to interactions between exclusive in utero maternal environmental factors and fetus susceptible genes may be the most important reason why maternal influence is greater than paternal influence during fetal and infancy periods.

Multiple postnatal environmental factors have been proven to be associated with increased risk of childhood asthma. As shown in Table 3, passive exposure to tobacco smoke increases the risk of allergen sensitization [81] and childhood rhinitis and asthma [60, 82–84], particularly when mothers are not atopic. Children exposed to traffic exhaust have increased risk of recurrent night cough and wheezing [85] and allergen sensitization in children with specific genetic polymorphisms [64], which may be associated with IgE-mediated asthma. In urban areas with high levels of vehicular traffic, the most abundant components of air pollution are airborne particulate matter, nitrogen dioxide, and ozone [86], which may explain the increased prevalence of asthma or allergic respiratory tract diseases in urban areas. Recent evidence has also revealed that allergic sensitization is positively linked to rhinovirus-related wheezing but not wheezing caused by other viruses [89]. Early exposure to acetaminophen [90] and broad-spectrum antibiotics [91] are also weakly associated with childhood wheezing or asthma. On the other hand, breastfeeding [87, 88] and exposure to farming environment

Table 3: Postnatal environmental factors associated with risk of childhood asthma.

Increased risk of childhood asthma	Decreased risk of childhood asthma
Environmental tobacco smoke exposure [60, 81–84]	Exposure to a farming environment [68]
Exposure to traffic exhaust and air pollution [64, 85, 86]	Breastfeeding [87, 88]
Rhinovirus-related wheezing [89]	
Early exposure to acetaminophen [90]	
Broad spectrum antibiotics used in early childhood [91]	
Early introduction of solid diet at infancy [67, 92]	

and animals with increased levels of microbial substances may protect against IgE-mediated allergic diseases [68]. A report of two prospective birth cohorts on the association of complementary foods with allergy stated that introduction of solid foods with a high diversity of different solids before the end of the fourth month may increase the risk of later allergy, particularly eczema. However, delayed introduction of solid foods beyond the sixth month of age or the avoidance of allergenic foods during the first year does not prevent allergy development [67]. These findings are also reflected in the new recommendation for allergy prevention published by the American Academy of Pediatrics [108] and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition [109]. Joseph and his colleagues reported a different finding that early introduction of complementary food before the age of 4 months is associated with a reduced risk of peanut (and perhaps egg) sensitization by the age of 2 to 3 years but only for children with a parental history of asthma or allergy [92]. Whether paternal or maternal atopy affects the postnatal environmental modulation of IgE production and asthma development remains to be determined.

6. Conclusions

The development of immunity and allergen sensitization is believed to start during the fetal period. CBIgE levels, reflecting antenatal IgE production, is significantly associated with total IgE levels, allergen-specific IgE levels, and even occurrence of asthma, according to most studies. However, the sensitivity and negative prediction rate are still unsatisfactory, making it a poor predictor of childhood asthma. Postnatal IgE, particularly after early childhood, is more sensitive and more relevant to clinical applications in aiding the diagnosis of IgE-medicated allergic diseases. The improvement of CBIgE application methods for predicting allergic diseases remains a big challenge.

Most studies have shown that both paternal and maternal factors have great impacts on IgE production and asthma development in the offspring. Genetic and environmental factors from both parents also contribute to this impact. This literature review revealed that maternal influence begins in the fetus and continues through infancy, childhood, and even adulthood, whereas paternal effect may not be apparent until early childhood, and the effect may increase with increasing age.

Asthma is a complex disease involving multiple genetic backgrounds and multiple environmental insults. Some specific genetic alleles may display greater effect in specific environments. Interactions of maternal oxidative stress genes (*GSTM1, GSTP1, CAT*, and *MPO*) with maternal prenatal exposure to air pollutants or tobacco smoke may contribute to asthma or allergic airway responsiveness. On the other hand, interactions of *TLR2, CD14* genotype, with farm exposure, and/or endotoxin exposure may protect against the the development of asthma. Experimental studies have revealed that most environmental factors manifest their effects on asthma development through epigenetic mechanisms, such as DNA methylation and histone modification. An increase in CpG methylation of the *IFN-γ* promoter and decrease in CpG methylation of the *IL-4* promoter have been observed in response to chronic exposure to diesel exhaust [74], and maternal prenatal exposure to PAHs has been linked to hypermethylation of *ACSL3* [75]. More studies are warranted to investigate the gene-environment interactions among maternal inheritance, paternal inheritance, and environment in perinatal stages for the prevention of IgE production and asthma development.

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Research Article

Gestational Medication Use, Birth Conditions, and Early Postnatal Exposures for Childhood Asthma

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Our aim is to explore (1) whether gestational medication use, mode of delivery, and early postnatal exposure correlate with childhood asthma, (2) the dose responsiveness of such exposure, and (3) their links to early- and late-onset asthma. We conducted a matched case-control study based on the Taiwan Children Health Study, which was a nationwide survey that recruited 12-to-14-year-old school children in 14 communities. 579 mothers of the participants were interviewed by telephone. Exclusive breastfeeding protected children from asthma. Notably, childhood asthma was significantly associated with maternal medication use during pregnancy, vacuum use during vaginal delivery, recurrent respiratory tract infections, hospitalization, main caregiver cared for other children, and early daycare attendance. Exposure to these factors led to dose responsiveness in relationships to asthma. Most of the exposures revealed a greater impact on early-onset asthma, except for vacuum use and daycare attendance.

1. Introduction

Asthma is a common childhood disease of complex etiology. Early-life environmental exposures are critical in determining susceptibility to asthma and allergic disease. Large epidemiological studies suggest that the key time period for the development of childhood asthma occurs between conception and 3 years old [1]. Both *in utero* exposure and early-life factors play important roles in the development of airway inflammation and hyper responsiveness [2]. The environmental factors that induce atopy may act together to affect the immune system, which later plays a part in the development of childhood wheezing or asthma.

Several prenatal, perinatal, and early postnatal risk factors have been reported to be related to childhood asthma. In the prenatal aspect, gestational Acetaminophen use might increase the risk of asthma [3]. In the perinatal aspect, some studies have shown that cesarean section causes an increased risk of asthma, but large population studies did not establish a clear degree of consistency [4]. Being born at gestational age of less than 37 weeks and having a low birth weight are well-known risks for asthma development [5]. In the early postnatal risk factors, issues regarding breastfeeding have yielded inconsistent results due to methodological differences and flaws in study design, the immunologic complexity of breast milk, and the possible genetic differences among patients [6]. Even age of daycare attendance might influence the risk of asthma [7]. Recurrent respiratory infections during early childhood also play an important role in asthma incidence [8]. Although several research papers have focused on environmental exposures for childhood asthma, few studies have discussed the influence of the timing of exposure and proved the exposure-asthma relationships in a dose-response manner. On the other hand, based on the background of popular use of herbal medicine during the pregnancy in Taiwan [9], we do not find any study exploring the relationship between gestational herbal medication use, and asthma.

In the present study, we explore in detail the relationships between early-in-life exposure to environmental factors such as gestational medication use, birth conditions, breastfeeding, daycare attendance, and recurrent respiratory tract infections and asthma in Taiwanese children. Our aims were to test (1) whether exposure in the environment to these factors would elevate the risk of asthma, (2) the dose responsiveness

of such exposure, and (3) their links to early- and late-onset asthma. We designed a case-control study using data from our previous Taiwan Children Health Study (TCHS) cohort.

2. Methods

2.1. Subject Selection. We conducted the present study focusing on the TCHS population. Details of the TCHS have already been described [10]. Briefly, the TCHS was a nationwide population-based study that recruited 5,804 seventh, and eighth-grade children from the public schools of 14 Taiwanese communities in 2007. A parent of each child provided written informed consent and completed a self-administered questionnaire. Data from the TCHS was considered baseline data.

A matched sampling design was used to select participants for this nested case-control study. Our study consisted of 4,982 of the 5,804 children, who were nonsmoking children aged 12 to 14 years old at the time of enrollment in the TCHS. Based on 3 age groups, 2 genders, and 14 communities, we then divided asthma- and wheeze-free children into 84 age-, sex-, and community-specific stratas. Controls were randomly selected based on a 1 : 2 principal according to the number of cases in each stratum. Therefore, our case group and the control group were matched by age, sex, and same community. In a structured telephone interview, the biological mothers of the participants were asked to provide details about their children, including demographics, family history of atopic diseases, gestational medication use, feeding practices in infancy, child's age when starting day care attendance, and episodes of respiratory infection events. Children unaccompanied by their biological mothers were excluded from our study population. Three well-trained field workers performed the telephone interviews by using standardized interview skills. All participants provided informed consent. The study protocol was approved by the Institutional Review Board at our university hospital, called the "National Taiwan University Hospital Research Ethics Committee", and we complied with the principles outlined in the Helsinki Declaration [11].

2.2. Exposure Assessment. With regards to prenatal exposures, we focused on detailed medication use status during maternal pregnancy, including different categories of medication and herbal medication as well. Medication tablet use was defined as medications which were prescribed by physicians and was categorized into hypnotics, antisemetics, antibiotics, tocolytic medication, analgesics, and medication for the common cold or gastrointestinal symptoms. General herbal medications for pregnant women in Taiwan, such as Bazhen Tang, Si Wu Tang, Ginseng, Coptis root, and anti-abortion herbs (An-Tai-Yin) were recorded. When the mother had a history of taking medication during pregnancy, we also asked about the time, frequency, and duration of the medication use.

As to perinatal risks, we were concerned about the modes of delivery, gestational age at birth and birth weight of the child. For those from vaginal delivery, we also asked whether vacuum or forceps were used. Preterm delivery was defined as birth before 37 weeks in gestational age, and low birth weight was defined as birth weight lower than 2500 gram. Special peripartum events and congenital defects were also recorded.

For early postnatal exposures, we gathered information about breastfeeding, respiratory tract infections, hospitalization due to respiratory tract infections and whether or not the main caregiver cared for other children in the child's first year of life. We encouraged the mothers to remember the diagnosis of the respiratory tract infections. Choices of respiratory tract infections included common cold, sinusitis, pneumonia, bronchiolitis, croup, acute respiratory distress syndrome, and unknown etiology. We also asked how early the child was sent to a daycare center. Upon determining ever-exposed status, we further inquired about the exposure duration and frequency, such as duration of exclusive breastfeeding, and times of respiratory tract infections and hospitalizations.

2.3. Case Definition. We distinguished asthma cases and controls by asking two questions: "Has your child ever experienced difficulty breathing, or have you observed any wheezing or whistling from their chest?" and "Has a doctor ever diagnosed your child as having asthma?" If the answers were "Yes" to both questions, we considered the child as an asthma case. If the answers were "No" to both questions, we considered the child as a control subject. We excluded those with inconsistent data to avoid information bias. Among the original 369 physician diagnosed asthma cases from our cohort, 287 cases were confirmed with "yes" to both questions during our telephone interview. We classified the age of onset as early onset (3 years old and below) and late-onset (after 3 years old) in order to reach similar numbers of participants in each group.

2.4. Statistical Analysis. For our matched case-control study design, we used conditional logistic regression to assess the risk of childhood asthma for each individual type of exposure. Odds ratios (ORs) and 95% confidence intervals represented the effects of each risk factor on developing childhood asthma. We further analyzed the different types of asthma by defining the asthma as early onset and late onset. ORs for the association of such exposures with early-onset and late-onset asthma were computed using the conditional likelihood method for multinomial logistic regression models. Chi-squared test of linear trend has been done to present the dose responsiveness. The missing information among these participants was also included in the model by using missing indicators [12]. Besides some a priori confounders based on previous research, we included a covariate if the estimate effects changed by at least 10% in confounder selection. All of the models were adjusted for the parents' level of education, family history of asthma, family history of atopy, mother's age at birth of this child, and *in utero* exposure to maternal smoking. Family history included the past atopy or asthma history of the parents. An independent T test was used to calculate the difference of mother's age at birth of this child between cases and controls. All tests were two-sided at

Table 1: Demographic characteristics of the study population.

	Case ($N = 193$)		Control ($N = 386$)		Control frequency corrected for sampling ($N = 4312$)	
Characteristics	N	%	N	%	$N^{\ddagger}$	%
Sex						
Girls	84	43.5	168	43.5	1876	43.5
Boys	109	56.5	218	56.5	2436	56.5
Parental education, yr[†]						
12	116	61.7	264	69.1	2603	60.4
13~15	41	21.8	69	18.1	888	20.6
16	31	16.5	49	12.8	821	19.0
Family history of asthma[†]						
No	165	89.2	372	97.9	4212	97.7
Yes	20	10.8	8	2.1	100	2.3
Family history of atopy*[†]						
No	101	54.6	274	72.1	3252	75.4
Yes	84	45.4	106	27.9	1060	24.6
In utero maternal smoking[†]						
No	189	97.9	382	99.0	4162	96.5
Yes	4	2.1	4	1.0	150	3.5

* Atopy is defined as allergic rhinitis or atopic eczema.
† Number of subjects does not add up to total N because of missing data.
‡ Predicted number of controls in the TCHS cohort based on the sampling.

a 5% significance level, and our study participant number was sufficient to reach 80% power. We used SAS version 9.1 (SAS Institute, Cary, NC, USA) software for our statistical analyses.

3. Results

Table 1 showed the demographic characteristics for all asthma cases and controls. Ultimately, 579 mothers were recruited in our study. 67.2% of the biological mothers of the 287 asthma cases in TCHS completely responded to our telephone interview. Of the 193 asthma cases, 91 (47.2%) were defined as early-onset and 102 (52.8%) were defined as late-onset asthma. We noticed that our control and original population were of similar frequency in sex, family history of asthma, and atopy (see Table S2 in supplementary material available online at doi:10.1155/2012/913426). The proportions of participants with a positive family history of asthma were 10.8% of asthma cases and 2.1% of the controls (Table 1). Similarly, asthma children had a higher probability of a family history of atopy (45.4%) than the control subjects (27.9%). The average age for the mother at birth of this child was 26.9 in case group and 28.4 in the control group ($P = 0.01$). For asthma children, 2.1% experienced *in utero* exposure to maternal smoking, while only 1.0% of the healthy group had been exposed to maternal smoking during the mother's pregnancy. This case-control study could represent the original cohort as we compared the frequency of control group to the control frequency corrected for sampling of the original population. Besides, our cases and original cases were of similar frequency in sex, family history of asthma, and atopy, and *in utero* maternal smoking (Table S3).

Exposure to medication or herbal medication during maternal pregnancy was positively associated with childhood asthma (Table 2). 18.9% of mothers among our participants had taken some kinds of medication tablets during their pregnancy. Among those taking medication, nearly two-thirds were medication tablets for the common cold. Any medication tablet use was associated with an increased odds of asthma (OR = 3.73; 95% CI, 2.2–6.33). Dose responsiveness on exposure duration was all significant (P for trend <0.05). The odds of asthma increased up to six times comparing to nonexposed group when the exposure occurred during the first trimester (Table 2). Taking medications for the common cold correlated with asthma positively (OR = 4.35; 95% CI, 2.28–8.3). The effect was greater for early-onset asthma as compared to late-onset asthma (OR = 5.31 versus 4.05). 58.9% of herbal medications taken by the mothers during pregnancy belonged to antiabortion herbs (An-Tai-Yin). We did not observe significant relationships between gestational herbal medication use and childhood asthma. However, this exposure correlated with early-onset asthma positively (OR = 3.63; 95%CI, 1.23–10.7) with significant dose responsiveness (P for trend <0.05).

Table 3 shows the impact of birth conditions on childhood asthma. Vacuum suction usage during vaginal delivery significantly influences the odds of asthma (OR = 3.68; 95%, 1.34–10.1). This impact was higher for late-onset asthma (OR = 5.16; 95% CI, 1.29–20.6). Additionally, being born before 37 weeks of gestational age was associated with

Table 2: Risks for childhood asthma in relation to gestational medication use.

Gestational medication category	Controls	Ever asthma			Early-onset asthma†			Late-onset asthma‡		
	N (%)§	*N*§	OR	95%CI	*N*§	OR	95%CI	*N*§	OR	95%CI
Any medication tablet¶										
No	350(90.7)	137	1.00		71	1.00		66	1.00	
Yes	36(9.3)	56	3.73	(2.2,6.33)**	20	3.64	(1.54,8.64)*	36	3.90	(1.96,7.75)**
Exposure time										
2,3 trimester	19(4.9)	20	1.80	(0.86,3.79)	7	3.37	(0.83, 13.63)	13	1.46	(0.58, 3.70)
1st trimester	17(4.4)	33	6.03	(2.91,12.5)**	12	3.32	(1.17, 9.43)	21	10.20	(3.34, 31.17)**
Exposure duration										
0–6 days	28(7.3)	43	3.46	(1.94,6.17)**	15	3.41	(1.31, 8.83)*	28	3.55	(1.69, 7.45)**
1 week	8(2.1)	13	4.86	(1.77, 13.37)*	5	4.57	(0.89, 23.56)	8	5.70	(1.43, 22.77)*
P for trend			<0.001			0.004			<0.001	
Medications for common cold										
No	351(93.6)	146	1.00		75	1.00		71	1.00	
Yes	24(6.4)	41	4.35	(2.28,8.3)**	13	5.31	(1.63,17.3)*	28	4.05	(1.85,8.87)**
Exposure time										
2,3 trimester	15(4.0)	17	2.19	(0.97,4.94)	6	4.76	(0.88, 25.90)	11	1.82	(0.67, 4.92)
1st trimester	9(2.4)	21	8.67	(3.10,24.23)**	6	4.49	(0.82, 24.48)	15	10.20	(2.78, 37.50)**
Exposure duration										
0–3 days	16(4.3)	23	3.19	(1.50, 6.79)*	8	4.50	(1.19,16.97)*	15	2.77	(1.08, 7.14)*
4 days	8(2.1)	18	7.83	(2.70,22.72)**	5	8.84	(0.83, 93.83)	13	7.17	(2.16, 23.75)*
P for trend			<0.001			0.008			<0.001	
Herbal medication										
No	361(93.5)	171	1.00		80	1.00		91	1.00	
Yes	25 (6.5)	22	1.59	(0.83,3.05)	11	3.63	(1.23,10.7)*	11	1.07	(0.44,2.61)
Exposure time										
2,3 trimester	8 (2.3)	8	1.41	(0.48, 4.09)	6	5.17	(0.89, 31.18)	2	0.53	(0.09, 2.95)
1st trimester	15 (4.2)	14	1.94	(0.85, 4.41)	5	2.99	(0.71, 12.54)	9	1.59	(0.57, 4.45)
Exposure duration										
<6 days	10 (2.7)	11	1.63	(0.63, 4.23)	7	6.83	(1.22, 38.13)	4	0.65	(0.17, 2.50)
1 week	14 (3.8)	11	1.77	(0.73, 4.28)	4	2.33	(0.58, 9.42)	7	1.96	(0.58, 6.59)
P for trend			0.12			0.05			0.46	
Exposure frequency										
<3 times/week	19 (5.1)	11	0.82	(0.35,1.94)	6	2.85	(0.68, 12.02)	5	0.41	(0.12, 1.41)
4 times/week	5 (1.4)	10	6.64	(1.89,23.32)*	4	4.71	(0.88,25.37)	6	16.70	(1.71, 162.76)
P for trend			0.02			0.02			0.14	

Models are adjusted for parental education, mother's age at birth of her child, parental history of asthma, parental history of atopy, and *in utero* maternal smoking.

*$P < 0.05$; **$P < 0.001$.

§Number of subjects does not add up to total *n* because of missing data.

†Early onset: asthma diagnosed ≦3 yr of age.

‡Late onset: asthma diagnosed >3 yr of age.

¶Any medication: including any medication tablet that physicians prescribed.

an increased odds of asthma (*P* for trend <0.05), especially the early-onset type.

The influence of early postnatal exposures on childhood asthma is outlined in Table 4. Exclusive breastfeeding showed a decreased odds of asthma (OR = 0.49; 95% CI, 0.31–0.79), especially for early-onset asthma (OR = 0.29; 95%CI, 0.13–0.65). Both recurrent respiratory tract infections (OR = 2.67; 95% CI, 1.78–4.02) and hospitalization in the first year of life (OR = 2.99; 95% CI, 1.58–5.67) were associated with increased odds of asthma, especially for early-onset asthma. Daycare attendance before the child was 3 years old correlated with greater odds of asthma (OR = 2.47; 95% CI, 1.33–4.57). However, this early-life exposure showed a greater influence on late-onset asthma (OR = 4.25; 95% CI, 1.55–11.7). Moreover, we found that the more children the caregiver raised in the first year life, the higher the odds of early-onset asthma (OR = 2.04; 95% CI, 1.13–3.69).

Table 3: Risks for childhood asthma in relation to delivery modes and birth conditions.

	Controls	Ever asthma			Early-onset asthma†			Late-onset asthma‡		
	N (%)§	*N*§	OR	95%CI	*N*	OR	95%CI	*N*§	OR	95%CI
Modes of delivery										
Vaginal	255 (66.2)	128	1.00		61	1.00		67	1.00	
Scheduled CS	58(15.1)	25	1.04	(0.59, 1.83)	13	1.19	(0.49, 2.88)	12	0.97	(0.45, 2.09)
Emergent CS	72(18.7)	38	1.13	(0.70, 1.83)	16	0.76	(0.37, 1.57)	22	1.63	(0.81, 3.28)
Forceps usage during vaginal delivery										
No	250(98.0)	118	1.00		59	1.00		59	1.00	
Yes	5(2.0)	9	2.12	(0.57, 7.91)	2	0.41	(0.04, 3.95)	7	5.10	(0.84, 30.93)
Vacuum usage during vaginal delivery										
No	243(95.3)	103	1.00		51	1.00		52	1.00	
Yes	12(4.7)	24	3.68	(1.34, 10.1)*	10	2.01	(0.47, 8.63)	14	5.16	(1.29, 20.60)*
Low birth weight										
No	338(90.4)	158	1.00		78	1.00		80	1.00	
Yes	36(9.6)	31	1.73	(0.96, 3.1)	13	1.99	(0.77, 5.13)	18	1.76	(0.81, 3.8)
2000–2500 gm	25(6.7)	22	1.70	(0.86, 3.35)	9	1.61	(0.56, 4.62)	13	1.60	(0.72, 3.55)
< 2000 gm	11(2.9)	9	1.79	(0.66, 4.87)	4	4.18	(0.65, 26.77)	5	5.69	(0.49, 65.67)
P for trend			0.08			0.10			0.09	
Preterm delivery¶										
No	356(92.2)	169	1.00		80	1.00		89	1.00	
Yes	30(7.8)	24	1.83	(0.98, 3.41)	11	2.47	(0.94, 6.50)	13	1.4	(0.63, 3.27)
34–36 wk	22(7.2)	16	1.74	(0.81, 3.74)	8	2.51	(0.82, 7.72)	8	1.16	(0.40, 3.36)
< 34 wk	2(0.7)	5	4.31	(0.81, 2.88)	3	4.80	(0.44, 52.14)	2	4.48	(0.39, 51.97)
P for trend			0.03			0.04			0.32	

Models are adjusted for parental education, mother's age at birth of her child, parental history of asthma, parental history of atopy, and *in utero* maternal smoking.

* $P < 0.05$.

§Number of subjects does not add up to total *n* because of missing data.

†Early onset: asthma diagnosed $\leqq$3 yr of age.

‡Late onset: asthma diagnosed >3 yr of age.

¶Preterm delivery was defined as children born at gestational age less than 37 weeks.

4. Discussion

Our findings suggested that the complex etiology of asthma could be traced back from *in utero*, perinatal to early postnatal period. In the present case-control study, we found that childhood asthma was positively related to a series of early-life events, such as *in utero* exposure to maternal medication/herbal medication use, vacuum use and being born before 37 weeks of gestational age during the perinatal period, recurrent respiratory tract infections, hospitalization, and daycare attendance in the early postnatal stage. Exposure to these factors led to dose responsiveness in the risk of asthma. Exclusive breastfeeding was negatively related with childhood asthma. To our knowledge, this is the first study which showed that gestational herbal medication exposures affected childhood asthma positively. Most of the exposures revealed a greater impact on early-onset asthma, except for vacuum use and daycare attendance. These early-life exposures may contribute to the earlier onset of childhood asthma. Several lines of evidence suggest that children who will go on to have more severe and persistent asthma symptoms already have first episode of airway obstruction in their infancy [13]. Hence, in order to prevent those relevant factors of childhood asthma, it would be important to distinguish different associated factors which will influence early- or late-onset of asthma more.

The safety of many common medications used in pregnancy has yet to be confirmed. According to a large prospective cohort study, medication use was reported in 39.2% of pregnancies and herbal medicine use was reported in 0.58% of pregnancies [14]. As compared to studies in Western countries, our prevalence of gestational medication use was lower (18.9%), but use of herbal medications during pregnancy was higher (8.1%). In the present study, we noted that the majority of medication tablets used during pregnancy were cold medications. Most cold medications contain a combination of decongestants, antitussives, expectorants, and mild analgesics which include acetaminophen

Table 4: Risks for childhood asthma in relation to early postnatal exposures.

	Controls	Ever asthma			Early-onset asthma†			Late-onset asthma‡		
Early postnatal exposures	*N* (%)§	*N*	OR	95%CI	*N*	OR	95%CI	*N*	OR	95%CI
Exclusive breastfeeding										
No	268 (69.4)	159	1.00		77	1.00		82	1.00	
Yes	118(30.6)	33	0.49	(0.31, 0.79)*	13	0.29	(0.13, 0.65)*	20	0.67	(0.37, 1.2)
Exclusive BF < 1 month	55 (14.3)	14	0.41	(0.21, 0.77)*	7	0.28	(0.10, 0.76)*	7	0.49	(0.20, 1.17)
Exclusive BF 1 month	63 (16.3)	19	0.60	(0.32, 1.11)	6	0.30	(0.09, 0.95)*	13	0.86	(0.41, 1.80)
P for trend			0.01			0.007			0.35	
Recurrent respiratory infections¶										
No	248(64.6)	79	1.00		33	1.00		46	1.00	
Yes	136(35.4)	111	2.67	(1.78, 4.02)**	56	4.07	(2.01, 8.27)**	55	2.26	(1.35, 3.81)*
Frequency										
3–6 times/year	91 (23.7)	46	1.55	(0.95, 2.53)	18	1.64	(0.68, 3.96)	28	1.64	(0.90, 3.02)
7 times/year	45 (11.7)	65	5.36	(3.12, 9.22)**	38	9.42	(3.84, 23.12)**	27	3.93	(1.86, 8.32)**
P for trend			<0.001			<0.001			<0.001	
Hospitalization within first year of age										
No	362(94.3)	163	1.00		73	1.00		90	1.00	
Yes	22(5.7)	30	2.99	(1.58, 5.67)**	18	4.04	(1.64, 9.96)*	12	2.24	(0.86, 5.83)
Frequency										
1 times	15(4.3)	23	3.56	(1.68, 7.51)*	12	3.53	(1.22, 10.24)*	11	3.40	(1.14, 10.10)*
2 times	5(1.4)	7	2.82	(0.84, 9.53)	6	12.21	(1.30, 115.07)*	1	0.62	(0.07, 5.80)
P for trend			0.001			0.002			0.29	
Daycare attendance within three years of age										
No	354 (91.7)	161	1.00		74	1.00		87	1.00	
Yes	32 (8.3)	30	2.47	(1.33, 4.57)*	17	1.77	(0.76, 4.12)	13	4.25	(1.55, 11.7)*
2-3 years old	17 (4.4)	18	3.12	(1.41, 6.93)*	9	1.70	(0.57, 5.03)	9	8.26	(1.94, 35.27)*
< 2 years old	15 (3.9)	12	1.85	(0.78, 4.40)	8	1.85	(0.59, 5.75)	4	1.90	(0.43, 8.34)
P for trend			0.02			0.20			0.03	
Main caregiver cared for other children										
No	231(59.8)	96	1.00		43	1.00		53	1.00	
Yes	155(40.2)	97	1.51	(1.02, 2.23)*	48	2.04	(1.13, 3.69)*	49	1.13	(0.65, 1.97)
Number of children||									
1	108(27.9)	67	1.42	(0.92, 2.20)	33	2.02	(1.04, 3.92)*	34	1.01	(0.55, 1.86)
2	47(12.1)	30	1.73	(0.97, 3.08)	15	2.10	(0.87, 5.06)	15	1.48	(0.67, 3.29)
P for trend			0.04			0.03			0.42	

Models are adjusted for parental education, mother's age at birth of her child, parental history of asthma, parental history of atopy, *in utero* maternal smoking.
* $P < 0.05$; ** $P < 0.001$.
§Number of subjects does not add up to total *n* because of missing data.
†Early onset: asthma diagnosed $\leqq$3 yr of age.
‡Late onset: asthma diagnosed >3 yr of age.
¶Recurrent respiratory infections were defined as more than three times of respiratory infections in the first year of life.
||The number of other children the main caregiver cared for in the first year of life.
BF: breastfeeding.

and nonsteroidal anti-inflammatory drugs (NSAIDs) [15]. Many studies have shown that prenatal exposure to acetaminophen may increase the risk of asthma, which was compatible with our findings with regards to cold medication use (Table 2). The possible mechanism of the association between acetaminophen and asthma has been hypothesized to involve the glutathione pathway which is downregulated following acetaminophen exposure [16].

The use of herbal medicine during the pregnancy period is common in Taiwan [9]. We surveyed some of the commonly used herbal medications in Taiwan, such as Bazhen Tang, Si Wu Tang, Ginseng, Coptis root, antiabortion herbs (An-Tai-Yin). Bazhen Tang and Si Wu Tang are used for better growth in fetus weight. Ginseng is used to avoid abortion in the early stage of pregnancy. Coptis root is taken to solve the skin problems of pregnant women and to enhance the beauty

of the skin of infants. An-Tai-Yin is used in pregnant women under risk of abortion to avoid abortion of fetus. We found that more than half of the herbal medications taken by the mothers during pregnancy belonged to antiabortion herbs (An-Tai-Yin). In a previous Taiwanese study, it was reported that An-Tai-Yin use during the first trimester was associated with an increased risk of congenital malformations of the musculoskeletal and connective tissues [17]. Until now, no study has been conducted on the relationships between gestational herbal medication use and asthma. In our study, we found that gestational herbal medication use was significantly associated with increased odds of early-onset asthma. The more frequent the herbal medication use by mothers, the higher the risk of asthma for their children (Table 2). Because of the incompletely assessed safety and efficacy of herbal medications, avoidance of herbal medicine during pregnancy should be recommended by obstetricians [18].

Reports on the relationships between cesarean section (CS) and childhood asthma are not consistent [4, 19]. "Hygiene hypothesis" suggested that the sterile infant is colonized by bacteria from the hospital environment and skin, not by maternal bacteria from the birth canal and perineum. Therefore, the initial "wrong" microbes can have long-term adverse effects on triggering atopic diseases [4]. Another possible mechanism is that CS is associated with increased risk of newborn respiratory distress syndrome, which might predispose to childhood asthma. Contrary to other studies [20], our result did not reveal a significant relationship between CS and childhood asthma. The results of this study were not consistent with the "hygiene hypothesis" and suggested that there might be a complex interaction between host and microbial agents with heterogeneous effects on the development of asthma [19].

In our data, vacuum-assisted delivery was associated with childhood asthma (Table 3), which was consistent with many previous studies [21]. Vacuum delivery is commonly indicated for prolong labor, maternal exhaustion, or emergencies at the delivery process. Maternal stress is related to excessive cortisol secretion, which further affects the child's immune system and increases the child's susceptibility to allergic disease [22]. In certain emergent circumstances, vacuum-assisted suction would be used in removing meconium aspiration, which could cause damage in lung of an infant. This pathological damage might lead the child to be more susceptible to having asthma in the future [23]. On the other hand, we found an inverse association between gestational age and childhood asthma, especially early-onset asthma. Our result was consistent with one recent meta-analysis based on 19 studies showing that children born prematurely would have an approximately 7% higher risk of asthma as compared with full-term children [5]. Another large population-based study suggested that this association was not solely due to prematurity increasing the risk of respiratory tract infection [24]. The exact mechanisms behind the links between preterm delivery and the development of childhood asthma need further investigation.

We found that exclusive breastfeeding prevents children from having asthma, especially for early-onset asthma (Table 4). The mechanisms for the effect of breastfeeding to protect infants from atopic diseases are quite complex. One is that soluble TGF-β, which is predominant in human breast milk, increases the ability of the infant to produce IgA against allergens. Soluble CD 14 in breast milk is thought to be the induction of a Th1 response to bacteria [25]. Another possible mechanism is related to childhood exposure to microbes. Breast milk may provide antiviral antibodies and other factors that reduce the incidence of these infections and subsequent wheezing. In a multicountry meta-analysis, breastfeeding was found to protect against only nonatopic wheezing in nonaffluent countries with OR of 0.69 (95% CI, 0.53–0.90) [26]. However, in another cluster randomized trial, results did not support the protective effect of prolonged and exclusive breastfeeding on childhood asthma [27]. Although our retrospective study design is prone to suffer from recall bias, it has been proven that maternal recall is valid and reliable in estimating breastfeeding initiation and duration [28]. Further extensive studies on the differences of mechanisms between exclusive and nonexclusive breastfeeding in relation to childhood asthma are warranted.

Exposures to recurrent respiratory tract infections and hospitalization in the first year of life were associated with increased odds of early-onset asthma. (Table 4) Early daycare would result in more respiratory infections early in life [7]. Infections with respiratory syncytial virus (RSV), parainfluenza, influenza, and rhinovirus are closely associated with the development of wheezing and pulmonary inflammation [29]. RSV-associated respiratory tract infections represented the most common cause of hospitalization at early infancy. In fact, numerous studies reported associations between RSV bronchiolitis in early childhood and recurrent wheezing and asthma in later childhood [30]. Our findings were consistent with these studies, but disputed the "hygiene hypothesis", suggesting the protective role of microbial infections during early childhood with regards to the development of asthma. Epidemiologic studies have challenged the "hygiene hypothesis" as being oversimplified [31]. One recent in vivo study suggested that innate immune stimulation via microbes could cause allergen sensitization in a dose- and time-dependent manner [32]. There might be complicated interactions between host and microbial agents in asthma development.

Recall bias is the major limitation in any case-control design. The mothers of children in the present study were informed that the interview was about the children's health problems, instead of explicitly mentioning asthma initially. Identification of asthma was performed at the end of the interview to reduce the possibility of recall bias. Distant recall of prenatal and perinatal factors reported by biological mothers has been considered a reliable approach in previous studies [33–35]. Githens et al. found 102 usable and reliable responses from mothers concerning gestational, perinatal and early-postnatal factors with a recall period of four to six years [35]. Yawn et al. also reported a high degree of agreement between medical records and maternal report for perinatal events such as cesarean section, preexisting diabetes, and smoking in a 10 to 15 years distant recall [33]. Moreover, in Buka et al.'s retrospective survey, women can accurately recall perinatal events such as CS, birth weight,

and length of gestation even after 22 years [34]. Furthermore, early-life environmental exposures in this study were not all well-known risk factors for childhood asthma, such as gestational medication use, herbal medication use, and vacuum delivery. The probability of a mother mistakenly recalling the early-life events during her pregnancy such as gestational medication use and her child's life should be comparable in both case and control groups, and a misclassification is likely to be nondifferential [36]. Moreover, significant dose responsiveness in many early-life exposures confirmed the importance of these risk factors. We believe that it is unlikely that a mother would have recall bias about the breastfeeding, hospitalization, and daycare attendance of her child [28, 37]. Given the rise in telephone scams in Taiwan today, the more educated mother in the healthy group tended to decline any telephone interviews from people they do not already personally know. Selection bias may exist in telephone interview process because less educated mothers in the control groups may be more willing to be interviewed. On the contrary, well-educated mothers of asthmatic children would be more willing to answer our 30 minutes telephone interview, because they cared about their child's health more. To compensate for this, we adjusted the level of education of the parents in our statistical models. On the other hand, we noticed that those mothers in our control group were of lower *in utero* smoking prevalence. This is because mothers who are willing to answer our telephone interview were those who cared about their children's health more. Therefore, *in utero* maternal smoking was chosen was a confounder to be adjusted in our statistical model.

5. Conclusions

Our data disclosed that gestational medication use, vacuum delivery, recurrent respiratory tract infections, hospitalization, and daycare attendance in early postnatal stage were associated with higher odds of childhood asthma. Exclusive breastfeeding protects children from asthma. Most of the exposures revealed a greater impact on early-onset asthma, except for vacuum use and daycare attendance. We recommend that mothers should be encouraged to breastfeed, to avoid any unnecessary medication during their pregnancy, and to protect children from harmful exposures in their early childhood.

Abbreviations

CS: Cesarean section
RSV: Respiratory syncytial virus
TCHS: Taiwan Children Health Study.

Author's Contribution

Dr. Yang-Ching Chen contributed to this submission in the areas of study design and also by writing the paper. Ms. Ching-Hui Tsai assisted with the statistical analysis. Professor Yungling Leo Lee supervised all of this work.

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Review Article

Perinatal Cat and Dog Exposure and the Risk of Asthma and Allergy in the Urban Environment: A Systematic Review of Longitudinal Studies

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Background. The literature is contradictory concerning pet exposure and the risk of development of asthma and other allergic diseases. Using longitudinal studies, we aimed to systematically review the impact of pet ownership in the critical perinatal period as a risk factor for allergies in childhood. *Methods*. Medline database was searched for urban cohort studies with perinatal exposure to cats and/or dogs and subsequent asthma or allergic disease. *Results*. Nine articles, comprising 6498 participants, met inclusion criteria. Six found a reduction in allergic disease associated with perinatal exposure to dogs or, cats or dogs. One study found no association. Two found increased risk only in high-risk groups. *Conclusion*. Longitudinal studies in urban populations suggest that perinatal pets, especially dogs, may reduce the development of allergic disease in those without a family history of allergy. Other unmeasured factors such as pet-keeping choices in allergic families may be confounding the association seen in these high-risk families, and further study is required.

1. Background

Allergic disease appears to be on the rise worldwide, and although an allergic family history is one of the strongest risk factors for childhood allergy [1], large international studies [2–4] which highlight geographical differences in allergy prevalence, strongly suggest that environmental influences also play a causal role. Although pets are known to aggravate asthma, allergic rhinitis, and eczema in sensitized individuals [5] controversy remains about whether early life pet exposure is a risk factor or a protective factor in their development. Current guidelines issued in Australia [6], the United States [7], and the United Kingdom [8], and by the Global Initiative for Asthma [9] all agree there is currently insufficient evidence to provide any recommendations in relation to pet-keeping in early life and the development of asthma and allergic disease because systematic reviews [10–13] and a meta-analysis [14] have reached different conclusions. Early reviews [10] found pet-keeping increased the risk of sensitization [10] and allergic disease [10, 12] with later reviews [11, 13] finding no effect. A recent meta-analysis [14] reported less risk of childhood asthma associated with cats, but increased risk with dogs.

These disparate findings may be partly explained by inclusion of articles with different study designs. To date, there are no randomized controlled trials (RCTs) on the effect of

pet exposure on allergic disease outcomes. In the absence of RCTs, the most valuable evidence is provided by longitudinal studies with a wealth of baseline data and frequent followups which enable assessment of pet exposure prior to the outcome of allergic disease. Despite this, all the current reviews have included at least two study designs (case control and cohort) [14] with the remainder also including cross-sectional studies [10–12].

Differences in the timing of exposures between studies may also provide a reason for varied results. It has been proposed that there are important windows of immune development [15] in which environmental exposures can either increase or decrease the risk of subsequent allergic disease development [16]. The perinatal period encompassing 20 weeks prior to birth until 4 weeks after is a critical time in developmental maturation of the immune system [17]. There is good evidence that the developing immune system in the fetus is susceptible to environmental influences and that immune development *in utero* is epigenetically regulated [17] with maternal exposures influencing the child's propensity for allergic disease [18, 19]. To date no reviews have limited assessment of pet keeping exposure at the critical perinatal period which may have a differential effect on risk than pet exposure at other periods of life. Lastly, another source of difference between studies is the varied study settings especially urban versus rural environment. A key relevant difference is the way in which pets are kept and the interaction between pets and other animals in rural settings. Hence, the clearest way to tease out the effects of cat and dog exposure on asthma and allergy in children would be to study this in an urban environment. None of the reviews have taken this into account.

Therefore, we have conducted a systematic review of longitudinal studies in urban environments to explore the relationships between cat and dog exposure in the perinatal period and subsequent asthma or allergy.

2. Methods

2.1. Inclusion Criteria

(i) Human.

(ii) Full-term infants.

(iii) Population based or allergy enriched sample.

(iv) Exposure to cat and/or dog presence or allergen levels measured and reported from 20 weeks prior to birth until 4 weeks after birth.

(v) Urban households only.

(vi) Outcome assessed and reported—any allergic disease (asthma/wheeze/eczema/allergic rhinitis/food allergy) or atopy/sensitization as measured by serum IgE (total or specific) or on Skin Prick Testing.

(vii) Longitudinal (cohort) studies.

The comparison groups were the children not exposed to pets within each study.

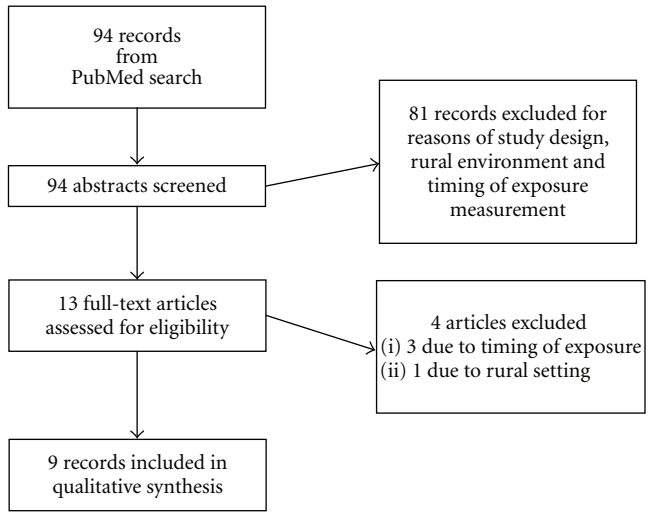

Figure 1: Flow chart of searching process.

2.2. Search Strategy. We searched Medline using the following strategy in PubMed. The last search date was 17 May 2011.

(i) One or more allergic disease outcome term: Allergy and Immunology "[Mesh] OR "Hypersensitivity" [Mesh]) OR "Asthma" [Mesh] OR "Respiratory Sounds" [Mesh] OR "Rhinitis" [Mesh] OR "Eczema" [Mesh] OR "Dermatitis, Atopic" [Mesh] OR "Immunoglobulin E" [Mesh]) OR "Bronchial Hyperreactivity" [Mesh]) OR "Food Hypersensitivity" [Mesh] OR "Allergens" [Majr]

AND

(ii) One or more pet exposure term: "Pets" [Mesh] OR "Animals, Domestic" [Mesh] OR "Cats" [Mesh], OR "Dogs" [Mesh]

AND

(iii) One or more age of exposure term: "Prenatal Exposure Delayed Effects" [Mesh] OR "Maternal exposure" [Mesh], OR "Fetus" [Mesh], OR "Infant, Newborn" [Mesh] OR "Birth"

AND

(iv) Study type-cohort, NOT review.

2.3. Process for Selecting Studies. A flow chart of the study selection process is shown in Figure 1. One author assessed all abstracts for eligibility. Full-text articles of eligible abstracts were then further assessed by the same author.

3. Results

Information concerning population, study type, exposure, outcome, and consideration of interaction by familial allergy for each of the nine studies is presented in Table 1.

Table 1

Study group, authors' name and year of publication	Population and study type	Exposure variable(s) and prevalence of pet-keeping	Outcome variable(s)	Familial allergy stratification	Findings
Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) Aichbhaumik, 2008 [20]	Unselected birth cohort in southeast Michigan Recruited women (21–49) in second trimester from Henry Ford Health System $N = 1258$ (1049 included in analysis)	*Pets* (*cats or dogs*) inside home at least 1 hr/day during pregnancy	*Cord blood IgE* $N = 1049$ (83%) Detection level $\geq$ 0.01 IU/mL	*Restricted* Excluded those families who selectively avoided pets because of allergy and still found reduced IgE in "low-risk" babies exposed to indoor pets	Infants in pet homes had decreased mean cord blood IgE 0.34 IU/L versus 0.24 IU/L $P \leq 0.001$ (similar for cats and dogs separately) Cord IgE higher in atopic/allergic mothers Serum IgE already higher in mothers with no pets
Prevention of asthma in children (PREVASC) intervention trial, Schönberger, 2005 [21]	Control group only of interventional birth cohort $N = 221$ (174 included in analysis)	*Dust samples* collected in 4th to 6th months of pregnancy from maternal mattress and living room Fel d 1 and Can f 1 levels were divided into quartiles	Days 3–5 after birth—*heel prick blood IgE* (total) Dichotomized at 0.5 IU/mL	*No*	Proportion elevated IgE increased with increasing HDM but not cat or dog
Copenhagen Prospective Study on Asthma in Childhood (COPSAC) and Manchester Asthma and Allergy Study (MAAS) Bisgaard, 2008 [22]	COPSAC: neonates (1 month) of mothers with asthma Birth cohort $N = 411$ (353 included in analysis) MAAS: Unselected birth cohort $N = 996$ (412 included in the analysis)	*Pet at home* On interview: cat or dog living in house at birth	*Age of eczema* COPSAC: physician diagnosed based on Hanifin-Rajka criteria: 1, 6, and 12 months. MAAS: parental report, ISAAC questions at 1 yr	*Filaggrin mutations* Homozygosity or heterozygosity to 2 (R501X and 2282del4)	In both cohorts found: FLG genotype increased risk of eczema in first year HR 2.26 (95% CI 1.27–4.00) COPSAC in presence of cat this increased to HR 11.11 (3.79–32.6) In the filaggrin mutation group the HR for cat exposure was 7.49 (2.37–23.7) MAAS-3.82 (95% 1.35–10.8) (no increased risk in those without mutation) In the filaggrin group the HR for cat exposure was 2.47 (1.09–5.62) Dog exposure protective HR for COPSAC but increased risk for MAAS (not as marked as cat) In filaggrin loss of function variants there is no increase in eczema without the presence of a cat at birth

Table 1: Continued.

Study group, authors' name and year of publication	Population and study type	Exposure variable(s) and prevalence of pet-keeping	Outcome variable(s)	Familial allergy stratification	Findings
*Childhood Origins of Asthma Study (COAST) University of Wisconsin Gern 2004 [23]	Selected on basis of parental aeroallergen atopy or physician diagnosed asthma or both $N = 312$ families Birth cohort (285 included in analysis)	*Cat or Dog at home* at child's birth	*Atopic Dermatitis*: physician diagnosed, during first year or at 1 year *Sensitization* Allergen-specific IgE values ≥ 0.35 kU/L at 1 yr Allergens: egg, milk, peanut, Dust mite (*D. pteronyssinus* and *farinae*), and *Alternaria* *Food Allergy*: allergen-specific IgE + historical reports from parents or physician documentation	*No* Parental allergy and asthma considered as confounder, not formally modelled for interaction despite finding that fathers with cat allergy less likely to keep cats, and dog ownership more likely if mothers not cat allergic	Dog exposure at birth was associated with reduced allergen sensitization (19 versus 33%, $P = 0.02$) and atopic dermatitis at 1 year (30% versus 51%, $P < 0.001$) Cat exposure was not associated No association of cat or dog exposure on food allergy Postnatal exposure to dogs modified immune development by enhancing IL10 and IL13 responses. P values 0.12 and 0.08
*COAST Bufford 2008 [24]	Same cohort with followup at 3 years $N = 312$ Birth cohort (275 included in analysis)	*Cat or Dog at home* at child's birth	*Atopic dermatitis* or *wheezing* in the past year	*No*	Dog at birth associated with current AD OR 0.35 (0.15–0.83) at 3 years Current wheeze at 3 OR 0.49 (0.25–0.95) No association with cats
Mothers of German Nationality Pohlabeln 2008 [25]	Unselected mothers from 5 hospitals in 3 cities in northwest Germany Birth cohort $N = 3132$ (1881 included in analysis)	*Cats and dogs at home* at birth	ISAAC questions *Physician diagnosed eczema or itchy rash* for more than 6 months or cracked earlobes *Physician diagnosed asthma or chronic bronchitis* *Physician diagnosed hay fever* All these were considered as ever rather than current *Allergic symptoms:* any of eczema/asthma/hay fever defined above	*All Stratified* by first degree relatives with a history of allergic disease (reported history of asthma, eczema or hay fever in parents or siblings)	Newborns without a family history of allergic disease had a lower prevalence of asthma and eczema at age 2 when their families kept a dog. OR 0.52 (0.33–0.83) The risk was modestly elevated in allergic families who kept a dog in the allergic OR 1.43 (0.95–2.15) No associations found for cats or other pets

Table 1: Continued.

Study group, authors' name and year of publication	Population and study type	Exposure variable(s) and prevalence of pet-keeping	Outcome variable(s)	Familial allergy stratification	Findings
Prevention and Incidence of Asthma and Mite allergy (PIAMA) Kerkhof 2005 [26]	Selected: allergy high-risk birth cohort 1327 children of allergic mothers 2819 children of nonallergic mothers (1027 included in neonatal analysis, 492 included in 12 month, 682 included in 4 year)	*Pets at home in last trimester of pregnancy*	*Total IgE from heel prick* neonatal screening *Specific IgE at 12 months and at 4 years* (HDM, cat, dog grass, milk, egg)	*Restricted* Stratified by "allergy status" of mother for reporting demographics but not analysed separately Also, excluded those families with pet avoidance or familial allergy—no change in associations (low-risk group only)	Dogs during pregnancy had less risk of high IgE at birth OR 0.5 (0.2–1.0) Cats during pregnancy and less cat sensitization at 12 months OR 0.6 (0.4–1.0)
Oslo birth cohort Nafstad 2001 [27]	Unselected 3754 children Birth cohort (2531 included in analysis)	*Pets in home at birth*	Survey assessed *bronchial obstruction, asthma, allergic rhinitis, and infantile eczema*	*Stratified* by parental atopy but found no change (parental atopy based on questionnaire concerning asthma and hay fever)	Less odds Asthma 4 yrs 0.7 (0.5–1.1) Allergic rhinitis 4 yrs 0.6 (0.4–1.0) Infantile eczema 6 months 0.7 (0.5–0.9)
Tucson Children's Respiratory Study (TCRS) Remes 2001 [28]	Unselected birth cohort—1246 healthy babies (1076 included in frequent wheeze analysis; SPT analysis included 737 (6 yrs), and 613 (11 yrs); IgE analysis included 829 (9 months), 534 (6 yrs), and 462 (11 yrs))	*Cat or dog at birth*	*Frequent wheezing*: >3 episodes of wheeze in the last year (from 1–13 years) *SPT at 6 and 11yrs* *Serum IgE at 9 months and 6 and 11* yrs (*alternaria*, HDM mix, Bermuda grass, careless weed, mesquite tree, mulberry tree, olive tree)	*Stratified* by parental history of asthma (asthma diagnosed in either parent)	Dogs at birth associated with less risk of developing frequent wheeze—seen only in children whose parents did not have asthma HR 0.47 (0.31–0.72) There was no increased risk in the parental asthma group No association with cats. Both nonatopic and atopic children with dogs at birth also had a reduced risk of wheeze. HR 0.47 (0.24–0.91) and HR 0.56 (0.32–0.98) Neither dog nor cat at birth associated with SPT positivity or IgE

*These articles are both from the same study group.

Abbreviations: HDM: house dust mite; IgE: immunoglobulin E; SPT: skin prick Test.

The nine included articles represented 9 different studies. There were two articles included from one study, with outcomes presented at both 1 year [23] and 3 years [24] of age. Additionally one article reported on the findings of two studies [22]. Six studies were population based and three were on children at increased risk of allergic disease. The numbers analyzed ranged from 174 [26] to 2531 [27], while the total population included across all studies was 6,498. Only one article reported pet exposure exclusively as quartiles of allergen levels in vacuumed dust [21]; all other articles simply recorded the presence of cats and/or dogs in the home.

The allergic outcomes reported included: eczema in 4 articles; asthma/wheeze in 3; neonatal IgE in 3; sensitization in 2; allergic rhinitis in 1; food allergy in 1, and allergic symptoms (combination of eczema, asthma and hay fever) in one. The definitions and ages at which these outcomes were assessed varied between studies.

When assessing the quality of observational studies, particularly for possible sources of bias, the importance of addressing the following essential areas has been highlighted [29]: appropriate selection of participants, appropriate measurement of variables, and appropriate control of confounding. An assessment of the quality of included studies with reference to these areas is presented in Table 2.

Selection of participants and measurements of exposure and outcome variables were not thought to be sources of bias in any of the studies. None of the studies commented on recall bias although most of them recorded a parental history of allergy (a possible source of bias) retrospectively. Most of the studies used questionnaires for collecting data, so that interviewer bias was not applicable. Where interviews were performed however, whether or not the interviewer was blinded to the pet exposure status was not mentioned. There was possible bias due to loss to followup in four articles which did not explore whether those missing were different from those remaining in the study [22, 24, 26, 27]. Included confounders varied between studies introducing a possible source of bias.

The studies were divided into two groups based on when pet exposure was recorded. There were three studies which reported prenatal cat and dog exposure, and nine which reported exposure to cat and dog in the neonatal period.

3.1. Exposure Recorded Prenatally [20, 21, 26]

3.1.1. Neonatal IgE. The main outcome from all three articles was the total level of neonatal IgE, measured from cord blood [20] or from the neonatal screening heel prick test at 3–5 days after birth [21, 26]. A lower level of IgE at birth was found in two articles [20, 26] if dogs [26], or cats or dogs [20] were kept during pregnancy. Both of these articles further restricted their analysis to a subgroup of low-allergy-risk infants and confirmed a lower level of neonatal IgE. The third article, which found no association [21] between neonatal IgE and pet exposure prenatally, was not strictly comparable having used levels of cat and dog allergens in dust as the measures of pet exposure.

3.1.2. Sensitization. Additionally one of the articles [26], which was based on a selected allergy risk population, found a lower risk of IgE sensitization to cat at 12 months in those children whose mothers had been exposed to cats during pregnancy [26].

3.2. Exposure Recorded Postnatally [22–25, 27, 28].

There were six articles which recorded postnatal allergen exposure [22–25, 27, 28]. Although these articles recorded pet or pet allergen exposure in the first 4 weeks of life, almost all mothers would certainly have also had exposure during pregnancy.

3.2.1. Eczema. Four articles reported eczema as an outcome, variably defined as infantile eczema [27], atopic dermatitis [23, 24], or physician diagnosed eczema [22] and assessed at 6 months [27], 1 year [22, 23], or 3 years [24] of age.

In three of these articles [23, 24, 27] (representing two studies), the risk of atopic dermatitis or infantile eczema was reduced for children exposed to dogs [23, 24] or pets [27] at birth. The Childhood Origins of Asthma Study (COAST) [23, 24] followed up a high-risk birth cohort and found a lower risk of atopic dermatitis by 1 year and at 3 years when exposed to dogs at birth. There was no association with cats. In an unselected population from Oslo [27], it was reported that pets at birth conferred less risk of infantile eczema by 6 months of age. When stratified by paternal atopy (asthma and hay fever) only the high-risk group still showed less atopic eczema risk.

In the other article [22] (representing two studies), the exposure groups were stratified by genetic/hereditary factors and the risk of eczema was increased only in the high-risk groups if exposed to a pet. Bisgaard et al. [22] identified children with either of 2 filaggrin- (FLG)-null mutations in both the Copenhagen Prospective Study on Asthma in childhood (COPSAC) and the Manchester Asthma and Allergy study (MAAS) birth cohorts. When exposed to cats at birth, children with a FLG null mutation had an increased risk of eczema in the first year: there was no convincing evidence for a similar relationship with dog exposure at birth.

3.2.2. Wheeze/Asthma. Three articles measured asthma or wheeze as an outcome [24, 27, 28]. The variables measured included current wheeze at age 3 years [24], bronchial obstruction or asthma at age 4 years [27], and frequent wheezing (>3 episodes per year) at ages 1–13 years [28]. All of these studies reported reduced odds or a reduced hazard ratio associated with a dog [24, 28] or with pets at birth [27]. No studies showed an association with cats alone.

Two of these three studies stratified by family history of allergy or parental asthma [27, 28], one [28] finding a risk reduction in the group without a parental history of asthma whilst the other found no change in risk [27].

3.2.3. Other Outcomes (Sensitization, Rhinitis, Food Allergy, or Combined Variable). There were three studies which

Table 2: Evaluating the role of bias in the included studies.

Study	Aichbhaumik [20]	Schönberger [21]	Bisgaard [22]	Gern [23]	Bufford [24]	Pohlabeln [25]	Kerkhof [26]	Nafstad [27]	Remes [28]
Methods for selecting study participants									
Appropriate source population	☺	☺	☺	☺	☺	☺	☺	☺	☺
Inclusion and exclusion criteria	☺	☺	☺	☺	☺	☺	☺	☺	☺
Methods for measuring exposure and outcome variables									
Appropriate exposure measurement	☺	☺	☺	☺	☺	☺	☺	☺	☺
Appropriate outcome measurement	☺	☺	☺	☺	☺	☺	☺	☺	☺
Methods to deal with design-specific sources of bias									
Recall bias	NI	NI	NA	NI	NI	×	NI	NI	NI
Interviewer bias	NI	NI	NI	NI	NI	NA	NA	NA	NA
Loss to followup	☺	☺	(1) ×	☺	×	NA	×	×	☺
Blinding	NA	NA	NI	NI	NI	NA	NA	NA	NA
Methods to control confounding									
Appropriate design	☺	×	×	×	×	×	×	☺	x
Appropriate analytical methods	×	☺	×	☺	☺	☺	×	×	☺
Statistical methods (excluding confounding)									
Appropriate statistics	×	×	☺	☺	×	☺	×	☺	☺
Conflict of interests									
Declarations of conflict of interests	☺	×	☺	×	×	×	×	×	×
Identification of funding sources	☺	☺	☺	☺	☺	☺	☺	☺	☺
NHMRC evidence grading (ref)									
Levels	III-2	III-2	III-2	III-2	III-2	III-2	III-2	III-2	III-2

NA: not applicable; NI: not described in article.
☺: adequate; ✓×: poor; ×: not done.

measured sensitization as an outcome. Two of these showed no association [28, 30] with pet exposure at birth, whilst the third reported reduced allergen sensitization at 1 year in those children exposed to a dog at birth [23]. One article [27] examined allergic rhinitis at age 4 years and found a reduced risk in children exposed to pets at birth which persisted in both groups following stratification for parental atopy.

Only one article reported on the outcome of food allergy. This study found no effect of cat or dog at birth on the risk of "confirmed food allergy" [23] (defined as specific IgE to egg milk or peanut of ≥0.35 kU/L and a convincing history).

One article [25] reported "allergic symptoms" at 2 years of age (physician diagnosed eczema, chronic bronchitis or asthma, or hay fever) and found a reduction in symptoms among the children of families without a history of allergic disease if they had kept dogs at birth. However in dog-keeping families with a history of allergic disease, a modest increase was found.

3.2.4. Summary of Results. Of the nine studies which were included, six [20, 23, 24, 26–28] found that the risk of allergic disease, or allergic sensitisation, was reduced in children who had been exposed to pets at or before birth. Dogs were associated with less risk of allergic outcomes in four [23, 24, 26, 28] of the six articles, while the remaining two found either pet to be associated with a reduced risk [20, 27]. Additionally one article reported a lower risk associated with cat exposure [26]. Only one small study ($n = 174$) failed to find an association [21].

Measures of familial allergy or pet avoidance were employed by four [20, 26–28] articles to account for the confounding aspects of pet-keeping choices. Limiting the analysis to the non-allergy-prone low-risk group did not change the associations in two articles [20, 26]. The remaining two articles [27, 28] stratified their analyses by familial high- and low-risk allergy groups. Subsequently, Nafstad et al. [27] found reduced odds of allergic disease

in both high- and low-risk groups, whilst Remes et al. [28] found the reduced risk of allergic disease in pet-exposed children was limited to the low-risk familial allergy group.

This finding was further supported by the remaining two articles [22, 25] which only presented results stratified by allergic predisposition. Both found that high-risk children had an increased risk of allergic outcomes in the presence of dog or cat exposure at birth.

4. Discussion

Overall we found that for children without a family history of allergy, owning a dog was protective against the development of allergic disease. By contrast the findings with regard to those with a family history of allergy were more difficult to interpret. A major confounding factor may be that pet-keeping behaviour is likely to be strongly influenced by the allergic status of the parents and siblings, as is the child's risk of allergic disease.

Further work assessing the impact of allergic status on owning a pet will be required to better understand whether this effect is due to a gene-environment interaction.

One of the problems in this field of research as outlined above is the inability to completely account for the confounding effects of pet-keeping choices made by allergic families. Families with allergic members are less likely to keep pets [31, 32], so it may appear that allergic disease is associated with not keeping pets. The lack of randomized controlled trials of pet-keeping, which would remove the confounding effect associated with pet-keeping choices in allergic families, makes the next best evidential study design a prospective birth cohort [33]. The ability of cohort investigators to manage the effects of confounding by familial allergy depends upon the validity and completeness of the information they have gathered concerning familial allergy and pet-keeping choices.

In this systematic review, we found that the treatment of confounding by familial allergy status varied greatly between articles (Table 2). Some of the articles limited their analyses to low-risk groups, which gave only the less interesting half of the picture. There was no uniform measure of familial predisposition, with some articles using only parental asthma, some using all first degree familial allergic disease or atopy and one study combining this with pet avoidance behaviour. The varied nature of the measurement of familial allergic predisposition made it less likely that a clear picture of the relationship between pet-keeping and allergic disease would emerge. The articles also differed in which factors they included in their analytical models as potential confounders.

Another problem with pooling studies for a systematic review is that they may measure outcomes at different ages. As part of a comprehensive systematic review, Chen et al. [11] grouped 21 birth cohort studies whose measured outcome of wheeze varied from 1 year [34] to 12 years [28]. The nature of wheeze at these two ages is very different. Over half of wheeze recorded in early childhood is transient [35–37]. Therefore, studies reporting wheeze/asthma outcomes in early childhood will identify many children who will not go on to have true asthma at school age and may be less specific in their findings than those which measure wheeze after six years of age. This was also an issue for our articles where three included articles measured wheeze at or before four years of age.

Other issues related to the studies in this systematic review were the possibility of attrition bias due to loss of followup was not always explored, recall bias for survey questions related to parental allergies was not mentioned by any of the articles, and, reporting bias might also have influenced which articles were identified. Also, due to the perinatal exposure criterion, other birth cohort studies including the Multicentre Allergy Study [38], which measured pet exposure at 6 months, but not during the first month of life, were excluded.

Compared to previous reviews which have yielded inconsistent results, the strengths of this review are that it has measured pet exposure at one time period, the perinatal period which is arguably a critical exposure window for immune system maturation; it has included only one study design, the cohort study which is the design with the most evidential weight in this field; it has included only urban populations, thus avoiding other potentially confusing exposures present in rural communities; it has also identified the important role of familial allergy in interpretation of any results.

In the current systematic review, we were unable to perform a meta-analysis on the included articles due to heterogeneity in timing and assessment of exposures and outcomes. Despite this, the findings appear to have similarities across articles.

5. Conclusion

This paper of longitudinal studies of perinatal cat and/or dog exposure in urban populations suggests that dog exposure may have a protective effect on the risk of allergic disease in low-risk populations. Unfortunately in children at high-risk of allergic disease, there is still no clear answer. Further longitudinal studies or randomised controlled trials, in which the effect of familial allergy on pet-keeping choices is clearly explored, are needed.

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Review Article

Perinatal Programming of Asthma: The Role of Gut Microbiota

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Perinatal programming, a dominant theory for the origins of cardiovascular disease, proposes that environmental stimuli influence developmental pathways during critical periods of prenatal and postnatal development, inducing permanent changes in metabolism. In this paper, we present evidence for the perinatal programming of asthma via the intestinal microbiome. While epigenetic mechanisms continue to provide new explanations for the programming hypothesis of asthma development, it is increasingly apparent that the intestinal microbiota plays an independent and potentially interactive role. Commensal gut bacteria are essential to immune system development, and exposures disrupting the infant gut microbiota have been linked to asthma. This paper summarizes the recent findings that implicate caesarean delivery, breastfeeding, perinatal stress, probiotics, and antibiotics as modifiers of infant gut microbiota in the development of asthma.

1. Introduction

Supported by evidence from farm lifestyle and endotoxin studies [1], the hygiene hypothesis has changed our understanding of the environmental origins of asthma and allergic disease. However, it fails to explain the coexisting epidemic in autoimmune disease or the high rates of asthma among the urban poor in the United States. This limitation has motivated the continued search for alternate explanations such as the microflora hypothesis [2] and the developmental origins hypothesis for health and disease (DOHaD) [3]. Originating as the Barker hypothesis, DOHaD or "perinatal programming" has been a dominant theory for the association between low birth weight and cardiovascular or metabolic disease in later life [3]. In this paper, we present evidence for the perinatal programming of childhood asthma, with a focus on the intestinal microbiome. We begin with a discussion and examples of perinatal programming and epigenetics, highlighting environmental exposures during the *in utero* and *ex utero* time periods that are potential stimuli for the early programming of asthma. More detailed discussion is provided on the postnatal development of immunity and its interaction with the intestinal microbiome, with evidence for the long-term impact of 5 perinatal exposures: caesarean section delivery, breastfeeding, antibiotics, probiotics, and perinatal stress.

2. Perinatal Programming of Disease and Epigenetics

The DOHaD hypothesis proposes that nutrition and other environmental stimuli or insults can influence developmental pathways during critical periods of prenatal, and postnatal development, and subsequently induce permanent changes in metabolism and disease susceptibility [3, 4]. While coined by Barker as the "fetal origins" hypothesis [5], the realization that human development extends into the postnatal period led to a change in nomenclature to the "developmental origins" hypothesis. "Programming" is another common term for the DOHaD hypothesis. The DOHaD approach was initially focused on early-life nutrition as a pathway for obesity and related metabolic abnormalities but has since been expanded to include the psychobiological effects of fetal and infant exposure to stress [3]. In fact, overexposure of the fetus to maternal stress and glucocorticoids has been proposed as an alternative to fetal undernutrition, to account

for the association between the prenatal environment and the development of cardiovascular, metabolic, and neuroendocrine phenotypes.

Based on evolutionary concepts, the DOHaD theory surmises that predictive adaptive responses of the fetus to *in utero* environmental cues promote a phenotype that is optimally suited for the postnatal environment [6]. If the prediction is correct, there will be a good match between the adopted phenotype and the postnatal environment. If the prediction is poor, there will be a mismatch between the phenotype produced and the environment experienced, resulting in negative health consequences. For example, constrained fetal or infant growth from malnutrition followed by enhanced nutrition during infancy or later childhood leads to metabolic abnormalities, such as insulin resistance. Other DOHaD-informed studies have detected smaller brain hippocampal volume (a risk factor for depression and psychopathology) in individuals who were born low birth weight and exposed to postnatal adversity [3].

Epigenetic mechanisms—the imprinting of environmental experiences on infant gene expression—are increasingly thought to be at the root of the DOHaD hypothesis [7]. Specifically, epigenetic modifications affect gene expression without altering DNA sequence. There is strong evidence that early environmental exposures can activate or silence genes by altering DNA methylation, histone acetylation and methylation, and chromatin structure [3]. Since these modifications regulate the degree of DNA coiling and accessibility for transcription, they determine gene expression. DNA methylation is the best-characterized epigenetic modification [4], occurring at cytosine-guanine dinucleotides (CpGs). Site-specific and regional changes in CpG methylation are often highly correlated with gene expression. Following DNA replication, the original pattern of CpG methylation is restored, ensuring the perpetuation of epigenetic information in replicating cells.

The epigenetic phenomenon is clearly demonstrated by evidence of diet-induced DNA methylation during mouse fetal development and subsequent changes to coat color and body weight in the offspring of mothers who consume a high-soy diet during pregnancy [8]. DNA hypomethylation has consistently been documented in rat models of intrauterine growth retardation [9]. In humans, assisted-reproduction studies have shown that inappropriate epigenetic reprogramming can increase the risk of some developmental syndromes [4]. Altered DNA methylation has also been observed in response to maternal undernutrition during pregnancy and following child abuse [9].

3. Perinatal Programming of Asthma

Since immune and lung development occur largely *in utero* and during early childhood [10], perinatal programming is a plausible pathway for allergic and respiratory disease [11, 12]. Indeed, fetal exposure to maternal smoking during pregnancy, separately from postnatal exposure to secondhand smoke, can increase risk for asthma in offspring [13, 14]. As described in the review by Hylkema and Blacquiere [13], evidence is accumulating to show that tobacco smoke can modify fetal lung development and immune function. Other intrauterine exposures, such as maternal stress or adherence to a Mediterranean diet (high in folic acid and antioxidants), are also known to modify the risk of allergic disease in the offspring [15, 16].

Recent studies show that prenatal exposures can activate or silence immune-related genes through epigenetic mechanisms. Breton et al. found significantly lower global methylation of DNA in young schoolchildren with *in utero* exposure to maternal smoking, with hypermethylation at specific gene loci [17], and several examples of diet-induced modification of DNA methylation have been provided in the recent review by Attig et al. [9]. For example, maternal folic acid supplementation has been found to increase methylation of the insulin-like growth factor 2 gene in offspring, and animal studies show that folic acid can prevent hypomethylation resulting from maternal undernutrition. While there is evidence that immune system development (specifically T-cell differentiation) is under epigenetic regulation [18, 19], and epigenetic changes (such as DNA methylation) have been found in children with asthma [20, 21], it remains to be determined whether epigenetic modifications mediate the effects of maternal smoking, stress, and diet on child asthma.

As noted earlier, the DOHaD paradigm is not limited to the *in utero* time period. This brings us to the main focus of our paper: the role of gut microbiota in the perinatal programming of asthma. Mounting evidence indicates that the continuous and predictable presence of commensal bacteria (microbiota) in the human intestine plays an important role in shaping the immune system during infancy [22, 23]. Indeed, studies have shown that commensal gut microbes interact with immune cells to create and maintain host tolerance, influencing both innate and adaptive immune responses [24]. As detailed in later sections of the current paper, this "microflora hypothesis" has been put forward as an example of early-life programming of allergy and asthma [24, 25]. A key characteristic of metabolic programming or imprinting is the need to distinguish primary "imprints" from secondary physiological alterations that arise in response to primary imprints. This requires evidence that primary imprints are present directly after the programming period as well as in later life [4]. With this criterion in mind, we attempt to advance the DOHaD thesis of asthma by presenting evidence on how early-life environmental modifications of the intestinal microbiome can result in permanent changes to microbiota composition and immunity.

4. Immune System Development and Gut Microbiota

Development of the immune system begins *in utero* and continues postnatally. Human lymphocytes first appear in the liver within several weeks of conception and are evident in the thymus by 10–12 weeks of gestation [26]. They are responsive to mitogen stimulation by the second trimester [27], and allergen-specific responses have been documented as early as 22 weeks gestation [28]. At birth, cytokine responses are dominated by T-helper cell type 2 (Th2) cytokines

[29], and many aspects of neonatal immune function remain immature, including Th1 cytokine production, T-cell signaling and effector functions, monocyte responsiveness, and antigen presentation by dendritic cells [30].

Pregnancy itself is associated with a transient depression of maternal cell-mediated immunity [31] and predominance of Th2 cytokines at the maternofetal interface [32], which are thought to protect the fetus from immunologic rejection by the mother [33]. The maternal environment during pregnancy promotes Th2 polarity in the fetal immune system, with transition to a nonallergic Th1 phenotype occurring after birth. If this transition is delayed or impaired during early postnatal life, there is an increased risk of atopic disease including asthma [30].

Following birth, maternal influence on the developing infant immune system continues through breastfeeding. Maternal antibodies (including IgG and IgA) are transferred in breast milk, providing passive immunity to offspring during infancy. Immune cells (neutrophils and macrophages) and cytokines (interleukins, TNFα, and TGFβ) are also present in breast milk, along with bactericidal enzymes and antiviral factors [34]. Nutrients and growth factors in breast milk have been shown to regulate the innate immunity [35], while fatty acid composition can modulate neonatal cytokine responses [36]. Despite the many protective factors transmitted in breast milk, it remains controversial whether breastfeeding is protective against asthma development in the infant. While several studies have shown that asthma risk is reduced in breast-fed infants [37–40], others claim there is no association [41, 42], and an inverse relationship has been demonstrated for children with maternal history of asthma [43, 44]. Wright et al. found that in school age children born to asthmatic mothers, longer duration of exclusive breastfeeding was associated with an increased risk of asthma [43]. These findings are supported by animal studies showing that breast milk can mediate the transmission of asthma risk from mother to offspring [45], possibly through the delivery of high concentrations of Th2 cytokines. Thus, while breastfeeding unquestionably provides nutritional and immunological benefits to the developing infant, its role in the perinatal programming of asthma remains controversial.

In addition to maternal immunogenic factors transferred during and after pregnancy, it is increasingly apparent that postnatal microbial exposure provides an essential source of immune stimulation. Colonization of the intestine begins during the birthing process, and mounting evidence indicates that these commensal bacteria play a central role in programming the neonatal immune system [23, 24]. For example, gut microbes have been shown to induce regulatory T cells that help guide the host's Th1/Th2 balance, and recognition of microbiota-derived peptides by mucosal receptors has been shown to enhance systemic innate immunity [24]. It has also been hypothesized that commensal gut microbes may produce metabolites capable of epigenetic modifications [46]; however, this remains to be proven experimentally. Microbial metabolites include short chain fatty acids [47], which could influence asthma development, since maternal and infant dietary fatty acid composition have been associated, albeit inconsistently, with childhood asthma [48].

Since the early 2000s, we have known that infants who ultimately develop allergic disease harbor a distinct gut microbiota [49, 50], and new evidence suggests this may also be true for asthma. Two birth cohort studies have reported that gut microbiota profiles in the first month of life can predict recurrent wheeze or possible asthma later in childhood [51, 52]. In particular, colonization with the pathogen *Clostridium difficile* has been associated with increased future risk of wheeze or asthma [51, 53]. Results from ongoing studies employing new "next generation" technologies are highly anticipated and promise to vastly improve our understanding of infant gut microbiota composition, including how it may contribute to asthma development. In parallel, researchers are increasingly focusing on exposures that influence the developmental programming of the intestinal microbiome.

5. Perinatal Programming of the Intestinal Microbiome

A groundbreaking international study has shown that adult gut microbiota can be classified according to a limited number of distinct microbial compositions or "enterotypes" that respond differently to diet and drug intake [54]. Enterotypes are likely established during early life, explaining why neonatal gut microbiota composition has a lasting effect on health and immunity [22]. Indeed, research has shown that gut microbiota profiles during infancy can predict overweight at school age [49], and accumulating evidence indicates that asthma prediction may also be possible [51, 52]. From the DOHaD perspective, these associations could reflect developmental "mismatch" scenarios, whereby disturbances to early-life gut microbiota cause the infant to be maladapted for future microbial exposures, leading to inappropriate immune responses that ultimately contribute to chronic disorders such as overweight or asthma. Consequently, there is growing interest in learning which environmental exposures influence microbiota development in the infant gut. The KOALA birth cohort studies in The Netherlands have identified several perinatal exposures that alter the intestinal microbiota at one month of age [55, 56]. In this paper, we have chosen to focus on 5 perinatal exposures, for which there is the most evidence regarding associations with the development of asthma (Table 1): caesarean section delivery, exclusivity of breastfeeding, use of antibiotics, use of probiotics, and perinatal stress.

5.1. Caesarean Section Delivery. The newborn's first microbial exposure is to maternal microbiota during birth, which lays the foundation for intestinal colonization. Caesarean section delivery prevents exposure to maternal fecal microbes, resulting in fewer intestinal Bifidobacteria and Bacteroides [57, 58]. In the absence of these commensal species, infants delivered by caesarean section are more frequently colonized by the asthma-associated pathogen *C. difficile* [56]. Studies have reported disturbed fecal microbiota profiles in caesarean section delivered infants beginning at 1 day after birth and persisting to 6 months of age [58–60], with one report documenting microbial

Table 1: Summary of perinatal exposures that may influence the programming of asthma via modification of infant gut microbiota.

Perinatal exposure	Effect on gut microbiota	Effect on asthma development
Caesarean delivery	Prevents exposure to maternal fecal microbes. ↓ Bifidobacteria and Bacteroides [57, 58], ↑ *C. difficile* [53, 56]. Differences may persist for years [58–61].	Increases risk of asthma [62]; recent studies inconsistent [53, 63, 64].
Breastfeeding	Confers beneficial gut microbiota through prebiotic properties [66] or direct transfer of bacteria [67, 68]. ↑ Bifidobacteria, ↓ *C. difficile* [56, 57, 65].	Protects against asthma [69–73], except when mother is atopic [43, 44].
Antibiotics	Suppresses commensal bacteria, permits emergence of *C. difficile* [22, 56, 77]. Disturbance may persist for years [78, 79]. Even indirect exposure is harmful [57].	Increases risk of asthma [80–83], except when parents are atopic [82, 88]. Even indirect exposure is harmful [55, 84–87]. Some studies may be confounded [91, 92].
Probiotics	Direct or indirect exposure beneficially influences gut microbiota composition [94–96].	Protects against asthma in animal studies [97, 98]; human trials inconclusive [100–103].
Perinatal stress	Causes transient and long-lasting changes to gut microbiota in animal studies [104–107].	Increases risk of asthma [114, 115].

"Indirect exposure" refers to exposure occurring via the mother, during pregnancy or lactation.

differences a full 7 years after delivery [61]. In their 2008 meta-analysis, Thavagnanam et al. reported a 20% increase of asthma in children born by caesarean section [62], but there is considerable heterogeneity among recent studies. For example, a UK medical record linkage study documented that caesarean delivery was not associated with hospital admission for asthma beyond age 1 [63], while a Canadian study found an association with asthma at age 9 though it was limited to first-time caesarean section only [64]. New evidence for the birth mode-microbiota-asthma pathway has recently emerged from a study employing mediation analysis to show that the effects of caesarean delivery on asthma development are mediated by *C. difficile* [53]. As this study was limited to just 5 bacterial species, it is likely that other yet-to-be-identified bacteria also contribute to this pathway for the perinatal programming of asthma.

5.2. Exclusivity of Breastfeeding. Following birth, exclusive breastfeeding confers "beneficial" gut microbiota to infants, including increased colonization by Bifidobacteria and reduced prevalence and abundance of *C. difficile* compared to formula-fed infants [56, 57, 65]. These benefits have been attributed to the prebiotic properties of human-milk oligosaccharides [66] or the transfer of intestinal bacteria from mother to infant through breast milk [67]. Indeed, new research indicates that breast milk contains a collection of bacteria more diverse than previously thought [68]. Concurrently, new studies around the world continue to find that breastfeeding protects against recurrent wheeze and asthma in later childhood [69–73]; however, these benefits may not apply when the nursing mother is atopic [43, 44]. This phenomenon may be related to microbiota, since the breast milk of allergic mothers has been reported to contain significantly lower amounts of Bifidobacteria compared with nonallergic mothers, and their infants have concurrently lower counts of fecal Bifidobacteria [74]. The DOHaD paradigm would describe this scenario as a dietary "mismatch", whereby infants of atopic mothers initially receive low amounts of Bifidobacteria via breast milk, followed by exposure to higher levels of dietary bacteria after weaning. Since Bifidobacteria influence early immune development (including IgA production and cytokine responses) [75, 76], infants who are not sufficiently exposed to Bifidobacteria in breast milk may have inappropriate immune responses to microbial exposures later in childhood, leading to atopic disorders including asthma.

5.3. Use of Antibiotics. After breast milk and other nutritional supplements, antibiotics are the next most commonly ingested substances by infants. Antibiotics affect colonization of the intestine by suppressing commensal bacteria and causing the emergence of asthma-associated pathogens such as *C. difficile* [22]. Research shows that antibiotic use in the immediate period after birth can severely alter gut microbiota in infants [56, 77], and evidence from long-term studies suggests that these perturbations could last for months, if not years [78, 79]. Indirect exposure is also relevant, since gut microbial diversity is reduced in infants born to mothers who received antibiotics during pregnancy or while breastfeeding [57]. In parallel, new studies continue to find that early-life antibiotic exposure is associated with increased risk for wheeze or asthma later in childhood [80–83]. This association is upheld when antibiotic exposure occurs *in utero* [84–86], during the neonatal period [87], or through breastfeeding [55]; however, two studies have demonstrated that the antibiotic-asthma association is limited to children who are not already genetically predisposed to the disease [82, 88]. Once again, this phenomenon may be related to microbiota, since infants of atopic mothers inherit low levels of commensal bacteria [74] such that antibiotic exposure would be relatively less disruptive than for infants with "normal" gut microbiota. Infants of atopic mothers may also be more frequently colonized by *C. difficile* [53, 89, 90]; therefore, emergence of this asthma-associated pathogen may not rely on antibiotic disturbance in these children.

Recently, two systematic reviews have emphasized that the association between antibiotic use and subsequent asthma development is subject to confounding by reverse causation (because antibiotic treatment often occurs in response to respiratory symptoms) and confounding by indication (because respiratory tract infections leading to antibiotic use may be the underlying trigger for asthma development) [91, 92]. Despite potential confounding in many of the studies reviewed, the authors acknowledged that a causal relationship between antibiotic exposure and subsequent asthma development remains plausible, since a significant pooled estimate of effect was observed for studies that adequately adjusted for respiratory infections [92]. Finally, if disturbance of gut microbiota is indeed the mechanism for the antibiotic-asthma association, then the timing, dose, and type of antibiotics are likely to be important. Future studies of large, prospective cohorts that address these details and adjust for respiratory infections are needed to definitively confirm the effect of antibiotic exposure on the perinatal programming of asthma.

5.4. Use of Probiotics. Along with a growing appreciation for the role of gut microbiota in immune development and health outcomes, there is increasing interest in the therapeutic potential of probiotics (live, nonpathogenic bacteria that confer health benefits when ingested) for asthma and other immune-related disorders [93]. Studies have shown that administration of probiotics to pregnant women, nursing mothers, or newborns can influence the establishment and composition of infant gut microbiota [94–96]. In parallel, probiotics have shown promising immunomodulatory effects in animal studies, where perinatal maternal supplementation [97] and direct supplementation of neonates [98] have been found to attenuate allergic airway responses in offspring. However, despite this evidence, clinical trials in humans have been highly variable. While there is reasonable evidence that probiotics may be useful in the treatment or prevention of allergic rhinitis [99], there have been no conclusive studies for asthma to date [100]. Recent reports indicate that probiotics had no effect on asthma development [101], airway inflammation [102], or asthma-related events [103]. Thus, while they clearly influence infant gut microbiota, it remains to be determined whether probiotics play a role in the perinatal programming of asthma.

5.5. Perinatal Stress. Infants constantly encounter new situations; some of these will induce more stress than others. There is intriguing evidence from animal studies that stressful events during infancy have the capacity to modify gut microbiota. Using rhesus monkeys, Bailey and Coe were the first to report that disruption of the mother-infant bond could alter the intestinal microbiota of infants [104]. This effect was transient, lasting several days after maternal separation, but the same authors later showed that moderate maternal stress during pregnancy could disrupt infant gut microbiota for six months or longer [105]. Rodent studies support these findings, showing that frequent maternal separation in the first weeks of life is associated with altered gut microbiota in adolescence [106, 107]. New research suggests that it may be possible to mitigate maternal stress-induced effects with prebiotic supplementation during the neonatal period [108]; however, epigenetic mechanisms might also be involved, since rat pups of mothers that exhibited more frequent grooming and licking were found to have differences in DNA methylation, compared to the offspring of less attentive mothers [109]. Although human intestinal microbiome changes have been noted following emotional stress in adults [110, 111], stress-microbiome pathways have not been explored in infants.

Solid evidence exists for the association of stress and asthma. As shown in several studies conducted by Miller and Chen, stressful life events and a harsh family climate in early life can have long-term effects, resulting in elevated proinflammatory cytokines and glucocorticoid resistance in adolescents [112, 113]. Studies of allergic immune profiles in cord blood indicate that prenatal maternal stress modulates fetal innate and adaptive immune responses [16]. In addition, maternal anxiety during pregnancy [114] or parental stress during infancy [115] have been found to increase the likelihood of asthma at school age. It remains to be seen whether gut microbiota, and/or epigenetic mechanisms, are involved in these associations.

6. Summary

In this paper, we have presented evidence for the perinatal programming of asthma via the intestinal microbiome—a relatively new perspective that has evolved alongside modern technologies for the study of microbial communities. While epigenetic mechanisms continue to provide new explanations for the DOHaD theory of asthma development, it is increasingly apparent that the intestinal microbiota plays an independent and potentially interactive role. Commensal gut bacteria are essential to immune system development, and exposures disrupting the infant gut microbiota have been linked to asthma. Well-designed prospective birth cohort studies will be required to fully characterize the longstanding impact of caesarean delivery, breastfeeding, antibiotics, probiotics, and perinatal stress on asthma development and to empirically validate the "microflora programming hypothesis" in this context.

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