Chapter 2
Allergic Disease Epidemiology

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Abstract Allergic disease represents a spectrum of disorders characterized by abnormal sensitivity mediated by IgE. Approximately, 25 % of the population in industrialized countries suffers from some form of allergic disease such as allergic rhinitis (AR) or hay fever, allergic asthma, food allergy, allergic skin inflammation, and anaphylaxis, particularly in children and young adults. The sequelae of allergies may present in many organ systems and the manifestations of allergic disease are often associated with symptoms at multiple sites. In order to facilitate the implementation of effective treatment and prevention strategies, it is important and necessary for clinicians and other involved personnel to understand the epidemiology of allergic disease. This chapter focuses on the epidemiology of allergies causing asthma, AR, chronic urticaria (CU), eczema, drug allergies, IgE-mediated food allergies, allergic conjunctivitis, Henoch–Schönlein purpura, and eosinophilic gastroenteritis.

Keywords Allergic disease · Allergen · Allergic rhinitis · Epidemiology · Meta-analysis

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2.1 Introduction

Allergic diseases are common and their incidence has been continuously rising with the developments in technology and increasingly severe environmental pollution. Allergic diseases have a large social and economic impact that include the costs of health care, lost work and school hours, and lower quality of life. This occurs not only in industrialized and developed countries but also in the vast impoverished areas around the globe (De Sario et al. 2013).

Statistics show that respiratory diseases have been increasing all over the world, especially allergic respiratory disease whose incidence is rising at an alarming rate (Hjern 2012). The World Allergy Organization (WAO) reports that approximately one of five people suffer from some form of allergic disease such as allergic rhinitis (AR), asthma, conjunctivitis, eczema, food allergies, drug allergies, and other severe allergic reactions. The incidence of allergic diseases among on-duty soldiers in Switzerland has increased nearly three times in the past 30 years (Braback 2012). In short, incidences of allergic diseases have been substantially rising around the world in both developed and developing countries (Dimitrov et al. 2014). Allergies, as an increasingly severe health problem, have become a great concern of both governments and individuals. Allergy has been called "the twenty-first century disease."

2.2 The Ubiquitous Allergens

A significant risk factor for the increasing incidence of allergic diseases is the pervasive presence of allergens (Hernandez-Cadena et al. 2015). Humans are exposed to 8500 kinds of compounds and approximately 2800 of them, including certain cosmetics, are contact allergens (Yue et al. 2009). That is, a large number, but only a few of these contact allergens, actually cause allergic reactions in clinical trials and reactions to inhalant allergens and important food allergens are actually rare.

Inhalant allergens and important food allergens in China are consistent with those reported in other countries (Wang and Zhang 2012). The common inhalant allergens in China include *Dermatophagoides pteronyssinus* (D.p.), *Dermatophagoides farina* (D.f.), Artemisia pollen, *Humulus* pollen, *Alternaria*, ash pollen, cypress pollen, ragweed pollen, birch pollen, cockroaches, *Platanus Hispanica* pollen, cocklebur pollen, house dust, *Cladosporium herbarum*, dog dander, cat dander, feather grass pollen, *Aspergillus fumigatus*, etc. The important food allergens include eggs, milk, peanuts, soybeans, shrimp, crab, and some nuts, grains, and fruits. A six-year survey on allergic diseases in Guangzhou (Sun and Zheng 2014), a city in south China, revealed that at least 15 types of allergens are common in Guangzhou: D.p. and D.f. are the most common among inhalant allergens, while egg and milk are the most common food allergens. The most common allergens vary among different age groups; 9–18 year olds are most allergic to

D.p., D.f., and *Blomia tropicalis*, 3–6 year olds are most allergic to eggs and those younger than 3 years of age are most allergic to milk (Sun and Zheng 2014). The rate of positive sIgE against D.p. among patients with positive sIgE against eggs or milk increases with their age (Sun and Zheng 2014). It has been reported that the most common inhalant allergens in Changsha are flour mite and D.p. and the most common food allergen is shrimp (Lu et al. 2011).

A few new allergens have been found in recent years. Smith et al. identified two cat-derived allergens: the taste gland protein Fel d 7 and the latherin-like protein Fel d 8 (Smith et al. 2011); Ma et al. first identified two IgE binding proteins: Tab a 1 and Tab a 2 (Ma et al. 2011; An et al. 2013) identified eight D.f. allergens; Ayuso et al. identified two novel shrimp allergens (Yue et al. 2009; Zhang and Zhang 2014) and a tropomyosin-like allergen of sea urchin (*Strongylocentrotus purpuratus*) (XP_001192266), which showed only 22 % sequence identity and 35 % similarity with Lit v 1 (ACB38288.1) (Bergon-Sendin et al. 2014). A new major allergen was isolated from dog urine and identified as prostatic kallikrein (Begum et al. 2012) and a closely related or identical protein was detected in dog dander. The recombinant form of prostatic kallikrein displayed similar immunologic and biochemical properties to those of the natural protein and bound IgE antibodies from 70 % of the subjects with dog allergy. The dog allergen kallikrein was also found to cross-react with human prostate-specific antigen, a key culprit in IgE-mediated vaginal reactions to semen (Begum et al. 2012). Thus, allergen exposure is very common (Torres et al. 2014).

2.3 The Epidemiology of Common Allergic Diseases

Allergic diseases occur in people of all ages, from newborns to the elderly, and often in those with a genetic predisposition. Allergic diseases are often characterized by immediate allergic reactions and are mainly manifested as respiratory allergies, skin allergies, digestive tract allergies and anaphylactic shock. Common clinical allergic diseases include asthma, AR, allergic dermatitis, food allergies, allergic conjunctivitis, allergic purpura, and eosinophilic gastroenteritis. Understanding the epidemiology of common allergic diseases would provide a reference for their prevention and treatment.

2.3.1 Asthma

The incidence of asthma has been growing rapidly since the 1960s: from 2 to 10 % in Switzerland; from 7.3 to 8.2 % in the US during 2001–2009 with 17,700,000 cases of adult asthma and 7,000,000 cases of child asthma recorded in 2010; and by 38 % in Italy in the 20 years from 1991 to 2010 (de Marco et al. 2012). According to WHO estimates, 235 million people in the world currently suffer

from asthma (Bergon-Sendin et al. 2014), with over 50 % of the adult cases and over 80 % of the infant cases caused by house dust mite, with 250,000 reported deaths (Begum et al. 2012).

Due to the variations in diagnostic criteria among the different epidemiological studies, the incidence of confirmed and suspected asthma varies among different countries. In addition, the incidence of asthma in some population groups may be significantly higher than in others. Statistics have shown that the risk of asthma increases with age and is negatively correlated with the education level of the parents but seems not to be correlated with household income (Hammer-Helmich et al. 2014). One-year observational study on 3761 Taiwanese children less than 12 years old indicated that the correlation between the incidence of asthma and a family member smoking plus family socioeconomic status is gender-specific (Strong and Chang 2014). Multivariate logistic regression analysis revealed that family member smoking might predict the risk of asthma in girls but not boys; girls in low-income households are more likely to have asthma (Strong and Chang 2014). In addition, the asthma risk in both boys and girls is negatively correlated with the education level of the father in Taiwan (Strong and Chang 2014). According to 2008 and 2010 statistics provided by National Health Interview Survey (Table 2.1), National Center for Health Statistics, the incidence of asthma increased in the black and white non-Spanish population in the US but decreased in other race and skin-color populations (http://www.cdc.gov/asthma/nhis/default.htm).

An epidemiological investigation of adult asthma in Asia indicated a similar increasing trend as seen on other continents (Song et al. 2014). The incidence of asthma in adult residents was < 5 % lower than that seen in European adults, while the incidence of asthma among elderly Asians was about 1.3–15.3 %, which is relatively high. This could be attributed to the aging of this population (extended life expectancy and/or reduced birth rate) and more attention should be paid to the problem of asthma among the elderly people in Asia. In China, the National Pediatric Asthma Collaborative Group carried out an asthma epidemiology survey from September 2009 to August 2010 on 463,982 children from 27 provinces, autonomous regions, and four municipalities. The result indicated that the total asthma incidence rate was 3.02 % (95 %CI, 2.97–3.06 %) in the major cities of China and the prevalence in two years (2009–2010) was 2.32 % (95 %CI, 2.28–2.37 %) (National Cooperative Group on Childhood, etc. 2013). The prevalence of asthma was significantly different among regions, cities, ages, and genders; it was higher in male children (3.51 %) than in female children (2.29 %), highest in preschool children (3–5 years old), highest in East China and lowest in Northeast China, and highest in Shanghai and lowest in Lasa. Nearly one-third of children with asthma were not diagnosed at an early stage or not diagnosed correctly, thus, treatment and management of asthma in children also awaits improvement (National Cooperative Group on Childhood, etc. 2013).

The causes of the increasing incidence of asthma are not clear but several hypotheses have been proposed. Western researchers believe that the rapid rise in asthma over the past three decades in Western societies has been attributed to

Table 2.1 Current prevalence of asthma among children and adults by sex, race/ethnicity, region, and family income

	Prevalence rate (%)[a]					
	All ages		Children		Adults	
	Total		Age 18		Age 18+	
Characteristic	2010	2006–2008	2010	2006–2008	2010	2006–2008
Total	8.5 ± 0.18	7.8 ± 0.2	9.4 ± 0.35	9.3 ± 0.4	8.2 ± 0.21	7.3 ± 0.25
Male	7 ± 0.23	6.9 ± 0.3	10.5 ± 0.52	10.7 ± 0.65	5.8 ± 0.26	5.5 ± 0.35
Female	9.9 ± 0.26	8.6 ± 0.35	8.2 ± 0.42	7.8 ± 0.6	10.4 ± 0.31	8.9 ± 0.35
White non-hispanic	8.1 ± 0.22	7.8 ± 0.3	8.2 ± 0.48	8.2 ± 0.65	8.1 ± 0.26	7.7 ± 0.35
Male	6.5 ± 0.29	6.8 ± 0.45	9.2 ± 0.75	9.5 ± 0.95	5.7 ± 0.32	5.9 ± 0.45
Female	9.7 ± 0.33	8.7 ± 0.35	7.3 ± 0.59	6.9 ± 0.85	10.3 ± 0.39	9.3 ± 0.5
Black non-hispanic	12.1 ± 0.55	9.5 ± 0.55	15.9 ± 1.07	14.6 ± 1.45	10.7 ± 0.64	7.8 ± 0.6
Male	10.8 ± 0.77	8.5 ± 0.8	18 ± 1.48	16.5 ± 1.65	7.6 ± 0.91	5.7 ± 0.85
Female	13.3 ± 0.71	10.3 ± 0.8	13.7 ± 1.49	12.7 ± 1.75	13.2 ± 0.8	9.5 ± 0.8
Other non-hispanic	8.2 ± 0.66	14.8 ± 2.15	9.5 ± 1.35	13.6 ± 2.75	7.6 ± 0.72	15.1 ± 2.65
Male	6.8 ± 0.75	12.1 ± 2.95	8.8 ± 1.55	14.6 ± 4.3	5.8 ± 0.97	11.2 ± 3.65
Female	9.5 ± 0.99	17.4 ± 3.15	10.1 ± 1.94	12.6 ± 3.85	9.2 ± 1.08	19.1 ± 4
Hispanic	7.3 ± 0.4	14.2 ± 1.85	8.1 ± 0.57	18.4 ± 3.8	6.9 ± 0.49	12.8 ± 2
Male	6.6 ± 0.56	11.3 ± 2.5	9.8 ± 0.82	23.6 ± 1.1	4.9 ± 0.7	7.0 ± 2.65
Female	8.1 ± 0.5	16.9 ± 2.4	6.3 ± 0.68	13.0 ± 3.8	9.1 ± 0.72	18.2 ± 2.85
Puerto Rican[b]	18.5 ± 1.88		19.5 ± 2.6		18.1 ± 2.55	
Male	18.9 ± 3.09		23.1 ± 4.17		16.8 ± 4.23	
Female	18.2 ± 1.77		15.9 ± 2.57		19.3 ± 2.55	
Mexican/ Mexican–American[b]	6.3 ± 0.43		6.9 ± 0.62		6 ± 0.55	
Male	5.7 ± 0.58		8.5 ± 0.86		4.1 ± 0.69	

continued

Table 2.1 (continued)

	Prevalence rate (%)[a]					
	All ages		Children		Adults	
	Total		Age 18		Age 18+	
Female	6.9 ± 0.64		5.2 ± 0.74		7.9 ± 0.95	
Region						
Northeast	8.8 ± 0.5		9.5 ± 0.74		8.6 ± 0.57	
Midwest	8.7 ± 0.4		10.2 ± 0.82		8.2 ± 0.45	
South	8.3 ± 0.29		9.9 ± 0.62		7.8 ± 0.33	
West	8.3 ± 0.36		7.8 ± 0.58		8.4 ± 0.44	
Ratio of family income to poverty threshold[c]						
0–0.99	11.2 ± 0.51		12.1 ± 0.92		10.7 ± 0.56	
1.00–2.49	8.8 ± 0.32		9.6 ± 0.59		8.5 ± 0.38	
2.50–4.49	8.2 ± 0.38		8.8 ± 0.63		8.1 ± 0.45	
4.50 and above	6.9 ± 0.31		6.9 ± 0.54		6.9 ± 0.36	

Source National Health Interview Survey, National Center for Health Statistics, CDC from 2006 to 2008 and March 1, 2012
[a]95 % confidence interval
All relative standard errors are < 30 % unless otherwise indicated
[b]As a subset of hispanic
[c] Missing responses imputed

numerous diverse factors including increased awareness of the disease, altered lifestyle and activity patterns, and ill-defined changes in environmental exposures (Gilmour et al. 2006). In addition, smoking and obesity have some correlation with asthma (Eriksson et al. 2015); children of smoking parents show a higher incidence of asthma than those of non-smoking parents and severe obesity is closely correlated with adult-female asthma (Jackson et al. 2013). Furthermore, the type and timing of microbial exposure also play an important role in the development of asthma (Wildfire et al. 2014).

The pathogenesis of asthma has not been fully clarified. Recent studies tend to consider asthma a multifactorial airway disease that arises from a relatively common genetic background interfaced with exposures to allergens and airborne irritants (Gilmour et al. 2006). It is believed to be correlated with allergy, airway inflammation, increased airflow resistance, and airway hyperresponsiveness (Gu and Zhao 2011) With the development of molecular biology in recent years, studies on asthma-related genes have made great progress. Asthma-related gene mutations have been found on chromosomes 2, 3, 5, 6, 7, 9, 11, 12, 13, 14, 17, and 19, but the specific relationship has yet to be defined (Gu and Zhao 2011). In recent years, a Genome-Wide Association Study (GWAS) has been performed on the studies of the pathogenesis of asthma. A correlation has been identified between mutations in Chromosome 17q21 and asthma in Chinese Han people (Li et al. 2012). It was also found that mutations in Chromosome 17q21 were associated with primary asthma in Northeast China Han children (Yu et al. 2014). Using the GWAS network analysis platform "Identify Candidate Causal SNPs and Pathway" (ICSNPathway), it has also been identified that four candidate Single Nucleotide Polymorphisms (SNP) sites (rs7192, rs20541, rs1058808, and rs17350764), four genes (*HLA-DRA, IL-13, ERBB2,* and *OR52J3*), and 21 related metabolic pathways correlate with incidences of asthma (Song and Lee 2013). A novel SNP (rs10044254) was identified correlating with down-regulation of *FBXL7* and increased sensitivity of asthmatic patients to glucocorticoids but emphasized that this is an important regulatory mechanism of sensitivity to glucocorticoids in children, however, not in adults (Park et al. 2014). Recent studies identified some genes that may correlate with total IgE in asthma patients (*CRIM1*, *ZNF71*, *TLN1,* and *SYNPO2*) and demonstrated a correlation between mite-specific IgE and SNPs near OPPK1 (may be related to D.p.-induced asthma) and *LOC730217* (may be related to D.f.-related asthma) (Kim et al. 2013). Understanding the pathogenesis of asthma and the reasons for its increased incidence may suggest more effective strategies for the prevention and treatment of asthma.

2.3.2 Allergic Rhinitis (AR)

AR is a common disease among children with an incidence of 15–25 % (Adamia et al. 2014) but is often overlooked, misdiagnosed, or mistreated. AR may lead to severe rhinitis and asthma and is a global health problem (Chiang et al. 2012). This disease not only causes nasal and non-nasal inflammation of the respiratory

Table 2.2 The prevalence of allergic rhinitis in adults and children in different cities in China

	Prevalence of allergic rhinitis (%)	
Cities in China	Adults	Children
Beijing	8.7	14.46
Shihezi		12.56
Urumqi	24.1	10.1
Hohhot		4.5
Xi`An	9.1	3.9
Chengdu	34.3	10.1
Chongqing	32.3	20.42
Wuhan	19.3	8.3
Changsha	16.1	
Guangzhou	7.83	14.1
Shenzhen		20.1
Harbin		4.9
Changchun	11.2	
Shenyang	15.7	
Shanghai	13.6	13.1
Nanjing	13.3	
Hangzhou	8.9	

system but also results in fatigue of the affected individual and hindered cognitive ability. Genetic factors, asthma, upper respiratory tract infection, use of antibiotics in the first year after birth, living in a grassy environment and exposure to dust, certain gas, or smoke are all risk factors for AR (Eriksson et al. 2012; Galffy et al. 2014). The most common allergens that cause AR are dust mite, pollen, herbs, *Alternaria solani* and, German cockroach (Yang et al. 2011).

Epidemiological data have shown a rapid increase in the prevalence of AR in the past decades (Yang et al. 2013). The incidence of AR was lower than 1 % in the 1920s and began to increase after the industrial revolution, slowly in the 1950s–1980s, but sharply since at least 1990 (de Marco et al. 2012). AR in wealthy African countries, Taiwan, and some Middle Eastern countries is even higher than that of Western Europe and North America (Katelaris et al. 2012). The prevalence of AR is strongly associated with asthma and the incidences of both are on the rise in both developed and developing countries (de Marco et al. 2012; Pesce et al. 2012; Sanjana et al. 2014). Regions with a high incidence of AR often show a high incidence of asthma as well (Khan 2014; Wang et al. 2012b); the incidence of asthma is < 2 % among AR-free individuals but is as high as 10–40 % among AR patients (Ozdoganoglu and Songu 2012). Also, the prevalence of comorbid allergic diseases decreased with age (Hong et al. 2012).

The incidence of AR is about 10–25 % around the world, 10–20 % in US and Europe combined, or 12–13 % of Americans and 23–30 % of Europeans (Ozdoganoglu and Songu 2012; Zhang and Zhang 2014). Eriksson et al. reported

in 2012 that the incidence of AR in Sweden increased to 28 % (lower in males than in females, 26.6 versus 29.1 %) and the incidence was 33.6 % for those aged 30–40 (Eriksson et al. 2012). The incidence of AR was reported as 8.7–24.1 % in China (Zhang and Zhang 2014) and another study more specifically reported a 9.1 % incidence in Northern China (Wang et al. 2012b). Available data indicated that despite variations in the prevalence of AR in different regions of China, the prevalence of AR has increased in both adults and children over the past two decades (Zhang and Zhang 2014) (Table 2.2). The incidence of AR in Batumi of Adjara was 15.3 % and higher in boys than in girls. This difference in the incidence of AR between genders was in consistent with results reported by Chiang WC et al. (Chiang et al. 2012). According to the 2008 Nutrition and Health Survey in the Philippines, the incidence of AR in this country was 20 %, similar between males and females, higher in rural areas than in urban areas, highest in the 40–49 age group, more prevalent in May and June of the year, and similar between coastal and inland areas (Abong et al. 2012). Understanding the epidemiology of AR in different areas would provide references for further study and prevention of this disease.

2.3.3 Allergic Dermatitis

According to the differences in manifestations, inducing factors and prognosis, common atopic dermatitis is divided into chronic urticaria (CU), eczema, cold urticaria, solar dermatitis, skin scratch disease, contact dermatitis, angioedema, drug allergy, and so on. In this section, we will introduce the epidemiology of some of the most common types of atopic dermatitis.

(1) **Chronic Urticaria (CU)**

Urticaria is a common inflammatory skin disease that affects approximately 20 % of the general population (Papadopoulos et al. 2014). According to the current EAACI/GA^{2}LEN/EDF/WAO guideline, urticaria can be classified into the following two subtypes: spontaneous urticaria (SU, including acute spontaneous urticarial and chronic spontaneous urticaria) and inducible urticaria (including cold urticaria, delayed pressure urticaria, heat urticaria, solar urticaria, symptomatic dermographism, vibratory angioedema, aquagenic urticaria, cholinergic urticaria, and contact urticaria) (Zuberbier et al. 2014). Chronic spontaneous urticaria (CSU), usually called CU, is the most common subtype of all forms of non-acute urticaria, and accounts for 25 % of the cases of urticaria (Losol et al. 2014). Although accurate data on the prevalence of urticaria are unavailable, it is estimated that 15–25 % of the US population are affected at some time of their lives with urticaria and that 33 % of all urticaria cases are considered to be chronic (Rance and Goldberg 2013).

CU is defined as a clinical course over more than six weeks, with an average disease duration between two and five years (Rance and Goldberg 2013) that mainly affects the skin and is caused by degranulation of cutaneous mast cells and/or basophils and the release of histamine and other inflammatory mediators such as

arachidonic acid metabolites, leukotrienes (LTC4, D4 and E4), prostaglandin D2, serotonin, acetylcholine, platelet activating factor, heparin, codeine, anaphylatoxins C3, C5a, quinones, and neurotransmitters released from cutaneous nerve endings (Criado et al. 2013). Food/food additives, drugs, psychological conditions, mosquito bites, autoreactivity, and alcohol consumption were the predisposing factors for CU (Wildfire et al. 2014). Genetic factors also play a role in occurrence of this disease, since 31.4 % of the patients with urticaria had a family history of this disease. Note that aspirin and other nonsteroidal anti-inflammatory drugs are the most common drugs that cause chronic urticarial (Losol et al. 2014). Molecular genetic mechanisms of CU have been studied in recent years. Losol P et al. (Losol et al. 2014) showed that genes involved in CU pathogenesis were those related to mast cell activation and histamine (including *FcεRI, HNMT, HRH1, HRH2, TNF-α, TGFβ1, ADORA3*, and *IL-10*), the arachidonic acid pathway (including *ALOX5, CysLTR1, LTC4S,* and *PTGER4*), HLA class I and II alleles, and other genes (*UGT1A6, CYP2C9, NAT2, ACE,* and *PTPN22*). Candidate genes and GWAS were used to further reveal the molecular mechanism of urticaria in order to provide molecular markers for the different types of urticaria and to find new therapeutic targets.

The majority of studies of CU show that it can occur in populations of all ages, with a typical onset in the third to fourth decade of life, and females are affected nearly twice as often as males (Losol et al. 2014). The incidence of CU is now up to 5 % in the general population and over 10 % in people that have certain allergies or skin diseases. 45–90 % of people with CU suffer from itching with no known cause, with women being four times more likely to suffer from itching than men (Rance and Goldberg 2013). About 40 % of CU patients experience concurrent angioedema (Losol et al. 2014). CU has a profound impact on quality of life and causes immense distress to patients, necessitating effective treatment.

(2) **Eczema**

Atopic dermatitis, also known as eczema, is a common childhood atopic disease associated with chronicity and impaired quality of life. Eczema affects about 10–20 % of children (mostly before 5 years old) and about 1–3 % of adults in the UK and the incidence of eczema has increased as much as threefold in the past 40 years (Adams et al. 2013). The International Study of Asthma and Allergies in Childhood (ISAAC) hase III study on the global variations in the prevalence of eczema symptoms in children indicated that for 6–7 year olds (data on 385,853 participants from 143 centers in 60 countries), the prevalence of current eczema ranged from 0.9 % in India to 22.5 % in Ecuador, with new data showing high rates in Asia and Latin America (Odhiambo et al. 2009). For 13–14 year olds (data on 663,256 participants from 230 centers in 96 countries), the prevalence ranged from 0.2 % in China to 24.6 % in Columbia, with the highest rates in Africa and Latin America. In both age groups, the current prevalence of eczema was lower for boys than girls (Odhiambo et al. 2009).

Eczema is a complex disease caused by multiple genetic and environmental factors. Genetic factors play a significant role in eczema. We postulated that eczema is also related to specific SNPs. The first GWAS reported noncoding

rs7927894 on 11q13 to be associated with eczema in German children (Esparza-Gordillo et al. 2009). It has been reported that 11q13 and the gene encoding filaggrin (*FLG*) are important in the pathogenesis of childhood eczema (Wang et al. 2012a; Ziyab et al. 2014). Filaggrin molecules and their metabolites are crucial for skin barrier functions as they organize the keratin filaments and maintain skin hydration. Filaggrin molecules are metabolized to their constituent amino acids when the relative humidity drops below 80 % and *FLG* mutation carriers display reduced synthesis of the osmolytic "natural moisturizing factor" intended to protect the skin from drying (Thyssen 2012). A systematic study pointed out that exposure to antibiotics in the first year of life, but not prenatally, was more common in children with eczema (Tsakok et al. 2013). It has been reported that eczema was associated with high parental educational level but there was no association with household income (Hammer-Helmich et al. 2014).

The incidence of eczema is still on the rise in both developed and developing countries and approximately one-third of children with severe atopic eczema also suffer from a food allergy, whereas food allergies are rare in adult patients (Wassmann and Werfel 2015). Eczema has been correlated with food allergies, however, this correlation is often over-emphasized. The prevalence of food allergies in children with eczema is estimated to be between 33 and 63 % (Santiago 2015) but it does not mean that the food allergies are the cause of the eczema. Food allergies seem to play a key role in eczema flares, especially in those children with moderate-to-severe disease. It is true that many foods, including eggs, peanuts, cow's milk, soy, tree nuts, fish, and shellfish, may aggravate eczema in infants and children, especially in the first two years of life (Ben-Shoshan et al. 2015) and elimination diets will likely be part of the treatment (Santiago 2015).

2.3.4 Drug Allergy

Drug allergy is any reaction caused by a drug with clinical features indicating an immunological mechanism. Each year, approximately 62,000 people in England are admitted in the hospital after experiencing a serious allergic reaction to a drug and up to 15 % of inpatients have a prolonged hospital stay as a result of an adverse drug reaction (Dworzynski et al. 2014). Analysis of patient safety incidents reported to the National Reporting and Learning System between 2005 and 2013 identified 18,079 incidents involving drug allergy including six deaths, 19 "severe harms," 4980 "other harms," and 13,071 "near-misses" (Dworzynski et al. 2014). In China, where there is a long history of traditional Chinese medicine use-age, herb-induced adverse reactions are also increasing, especially herb-induced allergies. However, the true incidence of drug allergic reactions in China is not known, probably due to under-reporting. Some people are never offered referral to specialist services and instead stay in primary care while others have their drug allergy managed by other health care disciplines. Therefore, only a small proportion of people are treated in specialist allergy centers.

Penicillin allergy remains the most common reported drug allergy affecting 10 % of the general population depending on the specific population evaluated (Albin and Agarwal 2014). Nonsteroidal anti-inflammatory drugs (NSAIDs) are the second most common cause of drug-induced hypersensitivity reactions and account for 21–25 % of adverse drug events (Karakaya et al. 2013). Allergic reactions to NSAIDs such as ibuprofen, diclofenac, naproxen, and aspirin are common (Nascimento-Sampaio et al. 2015). In particular, 21 % of people with asthma are affected by NSAIDs (Morales et al. 2014). About 35 % of people with CU have severe reactions to NSAIDs, involving angioedema and anaphylaxis after administration of NSAIDs (Karakaya et al. 2013). Anaphylaxis during general anesthesia occurs in one in 13,000 in France and one in 20,000–30,000 in Australia, and it is estimated by extrapolation that the incidence of anaphylaxis is 175–1000 reactions per annum in the United Kingdom (Krishna et al. 2014).

2.3.5 Food Allergy

Food allergy is a serious public health problem and studies of food allergy began in 1905. It is a reproducible adverse event that elicits a pathologic IgE-mediated or non-IgE-mediated reaction, leading to a variety of clinical symptoms that affect the patient's quality of life such as runny nose, itchy eyes, dry throat, rash, and breathing difficulties, or even fatal anaphylaxis (Dyer and Gupta 2013; Zukiewicz-Sobczak et al. 2013).

Although up to 170 kinds of foods have been proven to be able to cause allergic reactions, in reality, only a small number are responsible for most food allergies. Approximately, 90 % of all food allergies are caused by only eight types of foods: milk, eggs, peanuts, other nuts, fish, shellfish, soy, and cereals sensitizing at different frequencies (Zukiewicz-Sobczak et al. 2013). Among them, peanuts, tree nuts, finned fish, crustaceans, fruit, and vegetables account for 85 % of the food-allergic reactions in adults (O'Neil et al. 2011), while milk, wheat, fish, soy, and peanuts are the most common food allergens in children. Prevention of possible life-threatening allergies is not only an important medical issue but also a responsibility of the food industry and related supervisors. However, currently, there are no effective therapies for food allergies (Burks et al. 2012). The standard therapy for the treatment of food allergies is allergen avoidance and prompts treatment of allergic reactions that occur on accidental exposure (Umetsu et al. 2015). However, in reality, the problem of food allergies is a difficult one to control due to the increasing size of the food-allergic population.

Due to the differences in diagnostic methods, the reported rate of food allergies differs greatly among different countries. In recent years, the incidence of food allergies has been on the rise for unclear reasons but is likely due to a complex interplay between biologic, genetic, and environmental factors (Ezell et al. 2014) and may be due to the use of genetically modified products (Zukiewicz-Sobczak et al. 2013). Over the past 15 years, the prevalence of food allergy appears to have

doubled or even quadrupled in the US, UK, and China (Umetsu et al. 2015). It is estimated that approximately 220–250 million people worldwide have suffered from food allergies (Umetsu et al. 2015). Food allergy affects 4–8 % of children and 5 % of adults in the US, with the prevalence of peanut allergy alone being 1.8 % of adults in the US, 2 % of 8 year old children in the UK, and 3 % of young children in Australia (Umetsu et al. 2015). One survey suggested that there was a significant association between the incidence of food allergy and race, age, income, and geographic region (Gupta et al. 2011).

2.3.6 Allergic Conjunctivitis

Allergic conjunctivitis is the most common form of ocular allergy. Approximately, 40 % of individuals in developed countries suffer from allergic conjunctivitis (Chigbu and Coyne 2015). In the United States, allergic conjunctivitis constitutes over 90 % of all ocular allergies and approximately 50 % of Americans have had at least one allergic reaction in their lives, with approximately one-third of them having allergies of the eye (Chigbu and Coyne 2015). Allergic conjunctivitis is caused by exposure of conjunctiva to allergens leading to an immune response and a series of tissue- and cell-responsive diseases that are manifested to varying degrees with symptoms including red eye (the most common sign of allergy conjunctivitis), watery eyes (88 %), itching (88 %), redness (78 %), soreness (75 %), swelling (72 %), or stinging (65 %) (Almaliotis et al. 2013), and can affect school performance and work productivity (Chigbu and Coyne 2015). According to the pathological mechanism and clinical symptoms of the allergic response on the ocular surface, ocular allergies present with a variety of types such as seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal catarrh keratoconjunctivitis (VKC), giant papillary conjuntivitis (GPC), and atopic keratoconjunctivitis (AKC) (Almaliotis et al. 2013; Chigbu and Coyne 2015).

The incidence of allergic conjunctivitis has been on the rise in recent years, especially in developing countries, and can be partially attributed to increasingly severe environmental pollution, increased number of pets, the wearing of contact lenses, eye cosmetic use, and other factors (La Rosa et al. 2013). Due to different geographical environments and medical conditions, the incidence of ocular allergy in various regions is significantly different, from 5 to 22 %, and more recent studies report rates as high as 40 % (Almaliotis et al. 2013; Kumah et al. 2015). One questionnaire revealed that 396 12–13 year old children of a population-based sample in Sweden showed a 19.1 % incidence of allergic conjunctivitis and a 17.6 % incidence of AR with a 92 % correlation (Hesselmar et al. 2001). But in reality, the overall incidence is greater than reported.

In China, there is not a lot of data on the epidemiology of allergic conjunctivitis. Investigation on 6179 patients with moderate or severe allergic conjunctivitis showed that the central regions of China have the highest prevalence of allergic conjunctivitis (45.1 %) and in other areas including the north, south, southwest,

and central-north the prevalence was 8.0 %, 18.1 %, 1.06 %, and 18.1 %, respectively (Li et al. 2008). SAC, PAC, and VKC are the most common forms of allergic conjunctivitis in China, with SAC and PAC being the major types (74.4 %). The incidence of SAC is 22.3 % in children, significantly greater than in adults (8.3 %), while the prevalence of PAC and GPC is less than 10 % in children (Li et al. 2008).

(1) **SAC, PAC, and GPC**

SAC and PAC are the most common types of ocular allergy and are self-limited (Almaliotis et al. 2013). SAC, also called hay-fever conjunctivitis and is a seasonal variant of allergic conjunctivitis, usually occurs in the spring and summer and generally abates during the winter months (La Rosa et al. 2013). SAC is the most prevalent type of allergic conjunctivitis and is usually due to outdoor aeroallergens including pollen, grass, mold spores, and other outdoor seasonal antigens (Almaliotis et al. 2013). In the US, the most common pollen allergen is ragweed, while in China it is *Artemisia* pollen (Almaliotis et al. 2013).

Generally, PAC, which can occur throughout the year with exposure to perennial allergens, is the perennial variant of allergic conjunctivitis due to indoor airborne allergens (Almaliotis et al. 2013). The incidence and clinical symptoms of PAC are lower (3.5:10,000) and milder than that of SAC (Dart et al. 1986). Aeroallergens associated with PAC patients are dust mites, pet dander, feathers, and mold (Chigbu and Coyne 2015). Compared with SAC, PAC patients are reactive to house dust (42 vs. 0 %) and the clinical symptoms are more closely aligned with perennial AR (Goldberg et al. 1998). SAC and PAC originate mostly in childhood, with males being affected more often. The reactivity can gradually disappear after puberty but about 50 % of patients relapse at the ages of 18–35. At this stage, the incidence between males and females is similar.

In 1950, GPC was reported for the first time. This disease can be caused by limbal sutures, contact lenses, ocular prostheses, and limbal dermoids (La Rosa et al. 2013) and, thus, is classified as an iatrogenic disease not, an allergic disease. Data showed that 1–5 % of patients wearing rigid gas permeable contact lenses and 15 % of patients wearing soft contact lenses suffer from GPC, which is similar to VKC. Patients from 10 to 50 years old, especially men, have suffered prolonged courses of AKC but the most severe cases occur in 30–50 year olds (Rich and Hanifin 1985).

(2) **AKC and VKC**

AKC and VKC are characterized by chronic immune inflammation with T cell infiltration and may be sight threatening. The symptoms of AKC are more serious than other ocular allergies and can be exacerbated in summer and winter (La Rosa et al. 2013). AKC is considered the ocular counterpart of allergic dermatitis, or eczema (La Rosa et al. 2013). The main symptoms of AKC are itchy eyes, dry eyes, and chronic eyelid eczema, usually with superficial punctate keratopathy or keratohelcosis. A small number of patients may have complications including conjunctival scarring, trantas dots, posterior capsular opacification or uveitis, with severe complications potentially causing blindness (La Rosa et al. 2013). AKC can persist throughout life.

VKC accounts for approximately 0.5 % of allergic eye diseases (Sehgal and Jain 1994), generally has a course of 5–10 years, and is more common in warm climates and warm weather months (La Rosa et al. 2013). VKC commonly appears in spring, summer, and autumn, with the spring plant pollens being particularly allergenic. But some patients are affected all year round. VKC occurs more often in the tropics than in northern climates and rarely in frigid zones, thus, the disease is more prevalent in sub-Saharan Africa and the Middle East (La Rosa et al. 2013). Young people are typically affected, with onset at ages 10–20 in 60 % of VKC patients and those patients typically also have a history of seasonal allergies, eczema, or asthma (La Rosa et al. 2013). In Europe, the prevalence of VKC ranges from 1.2 to 10.6 cases per 10,000, although the prevalence of associated corneal complications is much lower (0.3–2.3 per 10,000) (La Rosa et al. 2013).

2.3.7 Henoc–Schönlein Purpura (HSP)

Henoch–Schönlein purpura (HSP), also known as anaphylactoid purpura or allergic purpura, is a common autoimmune and multisystem allergic disease and is a type III hypersensitivity mediated small vessel vasculitis characterized by a clinical tetrad of specifically palpable purpura, arthralgia, abdominal pain, and renal disease, with gastrointestinal and renal involvement more prevalent in older adults (Kurdi et al. 2014). Leukocytoclastic vasculitis accompanied by immunoglobulin A (IgA) immune complexes within affected organs is the cause of these manifestations (Gupta et al. 2015).

Despite these years of study on HSP, the underlying pathogenesis of HSP remains unclear. Although some cases lack a clear precipitating event, streptococcal infections, staphylococcal infections, vaccinations, medications, and insect bites have been implicated as possible triggers (Ha et al. 2015). In adults, medications are the most common triggers and the most frequently involved medications include antibiotics, angiotensin-converting enzyme inhibitors (ACEI), angiotensin-converting enzyme II receptor antagonist (AGIIR), and NSAIDs (Gonzalez et al. 2009).

The incidence of childhood HSP is on the rise with an annual incidence of 13–20 cases per 100,000 children < 17 years old (Yang et al. 2015). Severe cases are becoming more frequent and can lead to serious consequences if not treated timely and correctly. HSP predominantly affects children and is rare in the adult population (Gupta et al. 2015). Up to 90 % of cases are in children between 4 and 11 years of age (Gupta et al. 2015). The incidence of HSP in this age group is 8–20 cases per 100,000 children annually. Approximately, 50 % of patients are < 5 years of age, 75 % of patients are < 8 years of age, and 90 % are < 10 years of age (Bluman and Goldman 2014; Lim et al. 2015), compared to 1.3 cases per 100,000 adults annually (Kang and Park 2014). Boys are affected more often than girls (male-to-female ratio is 1.5:1) and the incidence was the highest in Caucasian people and the lowest in African–American people (Bluman and Goldman 2014).

HSP most commonly occurs in October, November, January, February, and March and is relatively rare in July, August, and September and, in 90 % of cases, HSP is most frequently associated with recent respiratory tract infections (Kurdi et al. 2014).

2.3.8 Eosinophilic Gastroenteritis (EG)

Eosinophilic gastroenteritis (EG) was first reported by Kaijser in 1937 (Ingle and Hinge Ingle 2013). EG is an uncommon gastrointestinal disease affecting both children and adults, and is characterized by varying degrees of focal or diffuse infiltration of eosinophils in the gastrointestinal tract in the absence of secondary causes (Martillo et al. 2015), with the percent of peripheral blood eosinophils increasing up to 15–70 % in 80 % of the patients. Because the ranges of eosinophil numbers seen in normal and abnormal gastric and intestinal mucosa are not standardized, it is difficult to define eosinophilic gastroenteritis (Martillo et al. 2015). EG is a progressive disease occurring in industrial countries with an incidence that has been rising over the last decade even though the overall prevalence of allergy-mediated gastrointestinal disease is rare (Raithel et al. 2014). It occurs at any age but most commonly presents between the third and fifth decades of life, with the incidence of EG in the US being about 2.5 cases per 100,000 adults (Verheijden and Ennecker-Jans 2010).

However, the exact etiology of EG is still unclear. Frequently, EG patients have a personal or family history of asthma or other allergic disorders. Data show that in some cases, EG has an association with parasitic infections, allergic mechanisms, or medications such as enalapril, rifampicin, and indomethacin (Hepburn et al. 2010; Raithel et al. 2014). More than half of EG patients have a history of asthma, AR, urticaria, or eczema and up to 62 % of cases are sensitized to foods such as milk, eggs, mutton, and sea shrimp (Raithel et al. 2014; Rodriguez Jimenez et al. 2011).

Eosinophilic gastroenteritis presents with nonspecific gastrointestinal symptoms and in almost one-third of cases has concomitant esophageal or colonic involvement (Reed et al. 2015). It remains difficult to treat, with high rates of endoscopy. Current treatment for EG lacks direct evidence but after dietary measures, i.e., avoid eating or having contact with potential allergens, some patients may become cured (Assa'ad 2009; Hommel et al. 2012). The symptoms of EG may be alleviated without extra treatment, indicating that EG may be either an allergic or nonallergic disorder (Ekunno et al. 2012). A few studies have reported that low-dose steroid therapy may be an effective treatment for chronic relapsing EG and this has become the preferred treatment for preventing grave complications like ascites and intestinal obstruction (Ingle and Hinge Ingle 2013). In most patients, the response to corticosteroids is rapid, however, immuno-suppressants, sodium cromoglycate, or leukotriene-receptor antagonists may be needed by patients treated long-term with corticosteroids (Famularo et al. 2011).

The increase in the incidence of these allergic diseases, which underlie the phenomena associated with allergic hypersensitivity to allergens, and the progress of knowledge in new fields such as immunology, molecular biology, and genetics in the past few years have led to an unprecedented increase in interest in the difficult field of allergy. Consequently, it is hoped that this knowledge will continue to be further expanded in the coming years.

2.4 Meta-analysis

In a narrow sense, meta-analysis is a systematic quantitative analysis of previous published studies and is essentially a summarization of multiple studies that have the same goals. It is an evaluation of the combined significance of multiple results, namely, it is a series of procedures to obtain a quantitative average conclusion and to answer certain questions by combining the results of several studies.

The idea of meta-analysis first emerged in the early 1930s and was initially applied to social sciences like pedagogy and psychology. In 1955, this method was first applied to medical science (Floyd and Ohnmeiss 2000). In 1976, Gene Glass was the first to name this method "Meta-analysis" and established a series of procedures and methods to obtain a representative conclusion, namely, to use statistical concepts and methods to collect, sort, and analyze multiple previous empirical studies so as to get a clear understanding of a certain issue of concern and complementing traditional review articles in this area of research (Sena et al. 2014). In the late 1970s, as medical science began to integrate some concepts of social and behavioral sciences, meta-analysis was introduced into medical science and subsequently emerged in the medical literature.

Given the importance of meta-analysis in evidence-based clinical decision-making, Chinese clinicians and scientific researchers began to pay attention to the results of meta-analysis based research, however, the overall quality is relatively low in both methodology and reports. Many problems are encountered during writing of a meta-analysis such as a low rate of complete document recall, failure to list excluded trials, unclear patient characteristics, diagnostic criteria and therapeutic ranges, lack of quality control before combining data, lack of monitoring and control of potential biased data, unstandardized statistical analysis, lack of quality assessment of original research data, lack of sensitivity analysis with alternative methods, lack of assessment of publication bias, and lack of evaluation of the application potential. The reasons for such deficiencies are due to a lack of sufficient understanding of this method, not knowing when and how to make a meta-analysis, and failing to follow the standardized procedure and writing format.

However, not all problems require a meta-analytical approach. Performing a meta-analysis only for the purpose of publishing a paper can hardly yield results of practical value. Early in 1987, Chalmers TC summarized the four aims of meta-analysis (Chalmers 1988): (1) to deal with inconsistencies between studies that may be caused by different levels of research, different subjects, and various

interfering factors; (2) to enhance statistical power. Some randomized studies may have too small a control group to yield a solid conclusion. Using meta-analysis, the statistical power of these studies can be enhanced; (3) to enhance specificity and accuracy. When the results of several similar studies do not agree with each other, meta-analysis can combine studies to obtain an average effect and generate a more definite conclusion from controversial or even contradictory findings, resulting in a conclusion that is more specific and accurate; (4) to answer new questions. Through meta-analysis, certain unclarified issues due to deficiencies in a single study can be revealed, which may guide future studies.

2.4.1 Meta-analysis Procedures

Meta-analysis follows certain procedural steps in order to come to a conclusion that is objective and convincing, and they are described as follows:

First, the problem to be solved shall be clearly proposed and a research program shall be developed. This is the beginning step of every meta-analysis; a detailed research program shall clarify the objectives of the meta-analysis and problems to be solved, establish a proper set of inclusion and exclusion criteria, plan ways to select databases for literature and key word searches and decide which statistical indicators will be used for data merging.

Second, related literature shall be collected. According to the purpose of the study, proper databases or other data sources shall be selected. An online and manual search shall be combined to comprehensively and unambiguously collect related data. Comprehensiveness is an important feature of meta-analysis, which means, besides published papers, the author shall also collect unpublished data through all possible means such as conference papers, abstracts, and unpublished clinical trials, as well as personally obtained information. Attention shall be paid to references of the collected literature: if some of the literature meets the requirements of the searcher but the data or some other content were not clear, the original author shall be contacted for important information so as to reduce publication bias. For clarity, the process of retrieving relevant literature shall be described in the most detailed way possible. Data source, keywords, and search strategy shall be explained to allow others to repeat the study and to ensure objectivity and reliability of the meta-analysis.

Third, all research results that are collected shall meet the inclusion criteria. All experimental studies that may potentially meet the requirements shall be evaluated for relevance to the content. Generally, determination of the studies to be included shall be performed independently by two persons and, when inconsistency occurs, a consensus shall be made through discussion or by referral to a third party.

Fourth, the quality of the included studies shall be assessed. Quantitative and qualitative assessment shall be made based on proper standards. To assess the quality of the included research, an evaluation of how well system errors and

bias were prevented during design and implementation of the experiments shall be performed. Rigorous experiments generate more reliable results, while low-quality studies may exaggerate the effect of interventions or have false negative results. There is currently no golden standard for assessing the quality of experimental studies, however, some criteria and scales may be useful in evaluation of randomized trials such as the Jadad scale that is often used for quality assessment by Cochrane systematic review. Using this scale, at least two researchers can independently evaluate the selected studies to avoid inclusion of research results of different qualities that may lead to inaccurate analysis results.

Fifth, data shall be extracted from the included literature. After comprehensively selecting the appropriate literature, related information shall be extracted. The characteristics of each study shall be noted such as experimental design (whether it is a randomized trial or not), research background, research methods, sample size, data measurement, and statistical analysis, allowing the included studies to be classified into several categories for comparison or analysis. It is important to design a data collection strategy with a proper design so that common information and characteristics of each study can be best represented. To ensure reliability of data collection, two or more researchers shall independently assess the selected data, and when inconsistency occurs, a consensus shall be made by discussion or by referral to a third party.

Sixth, the data shall be statistically analyzed. The five steps above are the preliminary work of meta-analysis and they are time-consuming but have a great influence on the results. Statistical analysis of meta-analysis is relatively easy and can be done with the help of the Review Manager (Revman) software developed by the Cochrane Collaboration group, which developed and maintains the Cochrane systematic review system. This system calculates the weighted average of included data and statistical values in a comprehensive manner. Effect variables can be a continuous variable of measurement data or a dichotomous variable of count data. The effect of a certain intervention is generally represented by the average value for continuous variables and by rate difference (RD), odds ratio (OR), and relative risk (RR) for dichotomous variables.

For different statistical values and different statistical assumptions, the method of meta-analysis varies. In the case of different statistical values, the methods of meta-analysis can be grouped into three categories: (1) The first category uses effect size as the statistical value and is well suited for independent studies that use continuous measurement data. Currently, this type of method is mainly used in social science (pedagogy, psychology, etc.), clinical medicine, and ecology and represents the size and direction of an effect or phenomenon. (2) The second category is mainly used in epidemiology, etiology, public science, and other medical sciences and the statistical value is the relative risk, hazard ratio, and risk difference. (3) The third category is the regression method that emerged in medical science in the late 1980s. The statistical value is the dose-response slope and this method is well suited for independent studies whose results are disaggregated data.

Before combining statistics, the included studies must be first tested for heterogeneity. If the results of the independent studies share a common effect size,

namely, the results are in good agreement, a fixed effects model shall be used such as the Mantel–Haenszel method, Peto method, or General Variance-Based method for statistical analysis. If heterogeneity exists among the results of different studies, namely, the size of the effect varies, aggregation of the data shall be performed with great caution. If the aggregated data is still of clinical significance despite heterogeneity, a random effects model shall be used for data aggregation such as the Dersimonian and Laird model for statistical analysis. Since the random effects model is more in line with reality, it is well recognized by analysts and has been widely used. If the heterogeneity is severe, its source should be identified and generally includes clinical heterogeneity, methodological heterogeneity, and statistical heterogeneity. Researchers may perform subgroup analysis based on the source of the heterogeneity, or sensitivity analysis or multiple regression analysis, in order to select the appropriate model for statistical analysis.

Meta-analysis is the aggregation of multiple studies but the results of such aggregation may be greatly affected by a single study whereby inclusion or exclusion of such a study would generate a completely different conclusion. In this situation, a sensitivity analysis to identify the key factors that affected the conclusion should be performed in order to find the reasons why different studies generate a different conclusion. Stratified analysis is the most commonly used method for sensitivity analysis, that is, the included studies are categorized into different subgroups according to certain characteristics of a study such as sample size, quality of methodology, inclusion of unpublished studies, etc. Combining of data can be first performed in each subgroup. Then, the overall effects and that of each subgroup can be compared.

Besides RevMan, many other software programs can be used for data processing of meta-analysis such as the free MIX software, the business software Comprehensive Meta-Analysis, Meta-Win, etc., and some statistical software also integrate programs for meta-analysis such as STATA, SAS, and WinBUGs.

Seventh, an analysis report can be made (possibly by diagrams). The analysis shall be evaluated and a conclusion can be made, namely, the significance of the results for related clinical practice and future studies shall be summarized. In essence, meta-analysis is an observational study so that interpretation of the results should be made with great caution. Many of those interested in meta-analysis pay the most attention to this final part of meta-analysis or even just go directly to this part, however, the actual clinical problems are very complex and a meta-analysis should not be expected to provide an absolute solution, thus, more information should be provided in this report. For example, the methodological quality and disadvantages of the included studies shall be explained and methodology of the meta-analysis itself, applicability of the results, and other information related to medical decision-making (pros and cons and cost of the intervention) shall be clarified. Results analysis shall also include assessment of the effect and explain the deficiencies in experimental design and data analysis, so as to guide future studies.

As can be seen, meta-analysis has a rigorous design and clear standard for literature inclusion: it systematically considers the effect of research method, outcome measure, categorization, and conclusion; it provides the measurement index

(aggregated statistic value) and a mechanism to quantitatively estimate the effect size so that the analysis results are highly objective and scientific; it improves the overall statistical capacity of the literature; and it considers the quality of independent studies.

Besides the above seven steps, many other details should be included to generate a high-quality meta-analysis. A series of international standards are gradually being established to evaluate and help improve the quality of meta-analysis such as the recently proposed MOOSE, QUOROM, PRISMA, etc. (Bello et al. 2015). By adhering to such uniform reporting formats, the author can not only improve the clarity of the meta-analysis but also avoid missing important information. In addition, such a format would make it easier for editors and reviewers to control the quality of meta-analyses so that meta-analyses can be more scientific and standardized and become a true high-level reference for clinical decision-making.

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