Introduction

Asthma is one of the most common chronic respiratory diseases, characterized by wheezing, cough, and bronchial hyperresponsiveness. It is believed to be a multifactorial disorder with a strong genetic component [1,2]. Interleukin-13 (IL-13) is a central effector cytokine of allergic inflammation. Huang et al. [3] found that a significant enhancement of both IL-13 transcripts and secreted proteins in the allergen-challenged bronchoalveolar lavage (BAL) compared with the saline-challenged control sites of asthmatic and rhinitic patients. Furthermore, in human subjects with asthma, the IL-13 concentration in peripheral blood was increased across disease severity in a stable state and was up-regulated at exacerbations [4,5]. Recently, Corren et al. [6] reported that lebrikizumab treatment in 219 adults who had inadequately controlled asthma was associated with improved lung function. These results strongly suggested that IL-13 had an important role in the pathogenesis of asthma and the IL-13 gene may be a susceptibility gene of asthma.

So far, a lot of studies investigated the association between the IL-13 gene polymorphisms and susceptibility of asthma [7–40]. Most of them focused on two polymorphisms: -1112C/T and +2044A/G. However, the results from these studies were inconsistent. Although two meta-analyses on these polymorphisms have been published [41,42], some inconsistent results still existed. For example, Yang et al. [41] reported that IL-13+2044A allele was associated with an increased risk of asthma among Asians but not among Caucasians. However, Cui et al. [42] found that IL-13+2044A/G polymorphism was associated Caucasians but not Asians. In addition, these two meta-analyses did not evaluate the association between IL-13 polymorphisms and atopic asthma. Hence, we performed a meta-analysis of all eligible studies to...
derive more precise estimation of the associations of IL-13 –1112C/T and +2044A/G polymorphisms with asthma risks. This was, to our knowledge, the most comprehensive meta-analysis of the association between IL-13 polymorphisms and asthma susceptibility.

Methods

Publication Search

Published studies were identified through a computerized search of Pubmed, EMBASE, Chinese National Knowledge Infrastructure (CNKI) and Wangfang databases (Last search was updated on October, 2012). The search terms were used as follows: (asthma or asthmatic) and (interleukin-13 or IL-13) and (polymorphism or mutation or variant). We also perused the reference lists of all retrieved articles and relevant reviews. There was no language restriction.

Inclusion and Exclusion Criteria

Studies included in the current meta-analysis should meet the following criteria: (1) evaluation of the polymorphisms in IL-13 gene and asthma risk, (2) using a case-control design, (3) genotype distributions in both cases and controls should be available for estimating an odds ratio (OR) with 95% confidence interval (CI). Studies were excluded if one of the following existed: (1) not relevant to IL-13 or asthma risk, (2) not designed as case-control studies, (3) genotype frequencies or number not offered, (4) non-clinical studies, (5) editorials, reviews and abstracts, and (6) not consistent with Hardy-Weinberg equilibrium (HWE). In the case of overlapping studies, only the one with the largest sample numbers was included.

Data Extraction

Data were extracted from all eligible studies independently by two of the authors (Nie and Liu). The relevant data were extracted into predesigned data collection forms. The following information was collected from each study: first author's name, year of publication, original country, ethnicity, age group, atopic status, sample size, genotyping method, and genotype number in cases and controls. We verified accuracy of data by comparing collection forms from each investigator. If a decision could not be made regarding inclusion, the full text of the article was examined.

Qualitative Assessment

Two authors (Nie and Liu) assessed the quality of each study independently. The quality scoring system was based on traditional epidemiologic considerations and asthma genetic issues [43]. Scores ranged from the lowest zero to the highest fifteen. Studies with quality scores ≤ 4 were defined as low quality studies [44].

Statistical Analysis

When the data from at least 3 similar studies were available, meta-analysis was performed. The strength of the association between the IL-13 polymorphisms and asthma risk was measured by ORs and 95% CIs. The statistical significance of summary OR was determined with Z test. OR1, OR2, and OR3 were calculated for the genotypes: 1). TT vs. CC (OR1), TC vs. CC (OR2), and TT vs. TC (OR3) for the -1112C/T polymorphism, 2). AA vs. GG (OR1), AG vs. GG (OR2), and AA vs. AG (OR3) for the +2044A/G polymorphism. These pairwise differences were used to indicate the most appropriate genetic model [45–47]. Once the best genetic model was identified, this model was used to collapse the three genotypes into two groups (except in the case of a
Table 1. Characteristics of the case-control studies included in meta-analysis.

| First authors/references | Year | Country     | Ethnicity | Age group | Atopic status | Case (n) | Control (n) | Genotyping method | Quality score |
|--------------------------|------|-------------|-----------|-----------|---------------|----------|-------------|-------------------|--------------|
| van der Pouw Kraan [7]   | 1999 | Netherlands | Caucasian | NA        | Atopic        | 101      | 107         | PCR-OLA           | 5            |
| Hakonarson [8]           | 2001 | Iceland     | Caucasian | Mixed     | Atopic        | 94       | 94          | PCR               | 10           |
| Howard [9]               | 2001 | Holland     | Caucasian | Adults    | Mixed*        | 171      | 119         | Sequencing        | 9            |
| Kauppi [10]              | 2001 | Finland     | Caucasian | NA        | NA            | 163      | 132         | PCR               | 7            |
| Leung [11]               | 2001 | China       | Asian     | Children  | Mixed*        | 157      | 54          | PCR-RFLP          | 9            |
| Xi 1 [12]                | 2004 | China       | Asian     | Adults    | NA            | 45       | 46          | PCR-RFLP          | 5            |
| Xi 2 [12]                | 2004 | China       | Asian     | Children  | NA            | 43       | 31          | PCR-RFLP          | 5            |
| Wu [13]                  | 2004 | China       | Asian     | Mixed     | NA            | 100      | 100         | PCR-RFLP          | 7            |
| Donfack 1 [14]           | 2005 | USA         | Caucasian | NA        | Mixed*        | 126      | 205         | DNAprint, LAS     | 9            |
| Donfack 2 [14]           | 2005 | USA         | African American | Mixed* | NA            | 205      | 183         | DNAprint, LAS     | 9            |
| Moissidis [15]           | 2005 | USA         | African American | Mixed | NA            | 61       | 157         | PCR-RFLP          | 5            |
| Zhao [16]                | 2005 | China       | Asian     | Children  | NA            | 130      | 100         | PCR-RFLP          | 7            |
| Kabesch [17]             | 2006 | Germany     | Caucasian | Children  | NA            | 73       | 773         | PCR-RFLP          | 9            |
| Battle [18]              | 2007 | USA         | African American | Mixed | NA            | 264      | 176         | PCR-RFLP          | 9            |
| Kang [19]                | 2007 | Korea       | Asian     | Children  | NA            | 374      | 242         | PCR-RFLP          | 11           |
| Chan [20]                | 2008 | China       | Asian     | Children  | Mixed         | 273      | 141         | PCR-RFLP          | 7            |
| Kim [21]                 | 2008 | Korea       | Asian     | Children  | Mixed*        | 715      | 240         | PCR-RFLP          | 10           |
| Black [22]               | 2009 | UK          | Caucasian | Adults    | NA            | 275      | 2453        | Tetra primer PCR  | 11           |
| Daley [23]               | 2009 | Australia   | Caucasian | Mixed     | NA            | 644      | 751         | Illumina          | 9            |

*Data for atopic or non-atopic asthma patients could be separately extracted.

PCR, polymerase chain reaction; OLA, oligonucleotide ligase assay; RFLP, restriction fragment length polymorphism; LAS, multiplex PCR and an immobilized linear array system; TaqMan-ASA, TaqMan allele-specific amplification method; IGGAS, Illumina GoldenGate Assay system; NA, not available.

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codominant model) and to pool the results. We used a random-effects model to calculate the pooled ORs. Heterogeneity among studies was examined with $I^2$ statistic. $I^2$ takes a value of 0–100% ($I^2 = 0–25\%$, no heterogeneity; $I^2 = 25–50\%$, moderate heterogeneity; $I^2 = 50–75\%$, large heterogeneity; $I^2 = 75–100\%$, extreme heterogeneity). A chi-square based Q-test was also performed to check the between-study heterogeneity, which was considered to be significant for $P_{\text{chi-square}} < 0.10$. To explore the source of the heterogeneity and evaluate the ethnic-specific, atopic-specific effects, subgroup analyses were performed by ethnicity and atopic status. To access the stability of the meta-analysis, one-way sensitivity analyses were carried out. We did cumulative meta-analysis by undertaking sequential random-effects pooling, starting with the earliest studies. Results were presented as a series of mini meta-analyses, which were ordered chronologically in a forest plot to show the consequence of adding studies on the effect size. Departure from HWE in controls was tested by the chi-square test. Publication bias was assessed by visual inspection of funnel plots, in which the standard error of log (OR) of each study was plotted against its log (OR). Funnel plot asymmetry was assessed by Egger’s linear regression test [48]. All statistical tests were performed by using the Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX). A $P$ value $< 0.05$ was considered statistically significant.

**Results**

**Study Characteristics**

The flow chart in Figure 1 summarizes this literature review process. In this current study, a total of 34 eligible studies met the inclusion criteria [7–40]. Four articles reported two cohorts [12,14,33,38], and each cohort was considered as a case-control study. There were 22 studies on -1112C/T polymorphism and 31 studies on +2044A/G polymorphism. There were 18 studies performed using Asians, 13 studies using Caucasians, and 4 studies using African Americans. Ten studies were performed in adults and seventeen in children. Seven studies included only atopic asthma patients, six studies included both of atopic and non-atopic asthma patients but data for these patients could be separately extracted, and 19 studies did not report detailed information. Quality scores for the individual studies ranged from 5 to 12. The characteristics of each study included in this meta-analysis are as follows.

**Table 2. Distribution of IL-13 genotype among patients and controls.**

| Studies | Asthma | Control | HWE |
|---------|--------|---------|-----|
| Van der Pouw Kraan | 31 | 13 | 77 | 28 | 7 | 0.765 |
| Howard | 99 | 63 | 9 | 87 | 30 | 2 | 0.748 |
| Wu | 50 | 37 | 13 | 69 | 25 | 6 | 0.087 |
| Donfack 1 | 72 | 42 | 12 | 126 | 71 | 8 | 0.607 |
| Donfack 2 | 69 | 100 | 36 | 66 | 85 | 32 | 0.009 |
| Moisidis | 13 | 36 | 12 | 62 | 75 | 20 | 0.712 |
| Kabesch | 34 | 33 | 6 | 471 | 263 | 39 | 0.770 |
| Battle | 95 | 126 | 42 | 58 | 85 | 30 | 0.005 |
| Kang | 236 | 128 | 10 | 156 | 79 | 6 | 0.276 |
| Kim | 455 | 236 | 25 | 155 | 80 | 6 | 0.246 |
| Black | 158 | 98 | 7 | 1609 | 673 | 80 | 0.353 |
| Daley | 425 | 195 | 22 | 490 | 234 | 27 | 0.886 |
| Li | 136 | 47 | 9 | 141 | 45 | 6 | 0.312 |
| Wang | 321 | 113 | 12 | 357 | 136 | 39 | 0.265 |
| Bottema | 67 | 43 | 5 | 65 | 23 | 4 | 0.301 |
| Dmitrieva-Zdorova | 149 | 116 | 18 | 117 | 94 | 16 | 0.623 |
| Undarmaa 1 | 190 | 117 | 18 | 227 | 98 | 11 | 0.915 |
| Undarmaa 2 | 230 | 121 | 16 | 459 | 196 | 21 | 0.989 |
| Yang XX | 144 | 43 | 6 | 148 | 50 | 6 | 0.048 |
| Baye 1 | 243 | 148 | 22 | 187 | 93 | 13 | 0.972 |
| Baye 2 | 115 | 151 | 48 | 18 | 25 | 8 | 0.889 |
| Munoz | 45 | 34 | 11 | 58 | 46 | 7 | 0.594 |
| i2044A/G | 3 | 25 | 66 | 3 | 27 | 64 | 0.941 |
| Hakonarson | 11 | 52 | 89 | 9 | 44 | 67 | 0.637 |
| Kauppi | 17 | 82 | 64 | 19 | 51 | 62 | 0.119 |
| Leung | 29 | 17 | 44 | 7 | 26 | 71 | 0.905 |
| Xi 1 | 149 | 116 | 18 | 117 | 94 | 16 | 0.623 |
| Xi 2 | 8 | 25 | 10 | 2 | 13 | 16 | 0.766 |
| Donfack 1 | 7 | 41 | 79 | 5 | 73 | 127 | 0.141 |
| Donfack 2 | 6 | 67 | 132 | 4 | 53 | 126 | 0.564 |
| Zhao | 52 | 60 | 18 | 50 | 42 | 8 | 0.842 |
| Battle | 9 | 81 | 17 | 5 | 52 | 117 | 0.787 |
| Kang | 48 | 166 | 160 | 28 | 100 | 101 | 0.673 |
| Chan | 43 | 136 | 94 | 17 | 70 | 54 | 0.431 |
| Kim | 90 | 318 | 301 | 28 | 100 | 99 | 0.724 |
| Black | 11 | 98 | 166 | 76 | 657 | 1729 | 0.161 |
| Daley | 22 | 196 | 426 | 21 | 209 | 520 | 0.999 |
| Jiang | 2 | 2 | 20 | 1 | 5 | 18 | 0.422 |
| Llanes | 2 | 38 | 68 | 4 | 54 | 87 | 0.194 |
| Wang | 49 | 194 | 203 | 59 | 234 | 212 | 0.646 |
| Feng | 10 | 19 | 17 | 3 | 10 | 30 | 0.128 |
| Bottema | 6 | 51 | 57 | 3 | 24 | 62 | 0.721 |
| Dmitrieva-Zdorova | 23 | 116 | 144 | 17 | 85 | 125 | 0.630 |
| Palikhe | 56 | 200 | 207 | 50 | 174 | 206 | 0.158 |
| Undarmaa 1 | 36 | 144 | 145 | 34 | 149 | 156 | 0.856 |
| Undarmaa 2 | 39 | 162 | 166 | 65 | 289 | 322 | 0.989 |

**Table 2. Cont.**

| Studies | Asthma | Control | HWE |
|---------|--------|---------|-----|
| Wu XH | 36 | 111 | 105 | 18 | 84 | 125 | 0.465 |
| Yang LF | 47 | 60 | 71 | 19 | 66 | 73 | 0.497 |
| DeWan | 5 | 34 | 65 | 23 | 171 | 309 | 0.915 |
| Baye 1 | 26 | 157 | 230 | 14 | 101 | 183 | 0.989 |
| Baye 2 | 8 | 87 | 220 | 1 | 14 | 36 | 0.787 |
| Noguchi | 113 | 438 | 387 | 232 | 1033 | 1111 | 0.718 |
| Munoz | 21 | 52 | 17 | 23 | 65 | 23 | 0.071 |

HWE, Hardy-Weinberg equilibrium.

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**Figure 2. Meta-analysis for the association between asthma risk and the IL-13 –1112C/T polymorphism.**

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**Table 3. Determination of the genetic effects of IL-13 polymorphisms on asthma and subgroup analyses.**

| Polymorphisms       | Study                   | Sample size | No. of studies | Test of association | Model | Heterogeneity |
|---------------------|-------------------------|-------------|----------------|---------------------|-------|---------------|
|                     |                         |             |                |                     |       |               |
|                     |                         | case        | control        | OR (95% CI)         | Z     | P Value       |
| −1112C/T            |                         |             |                |                     |       |               |
| TT vs. CC           | Overall                 | 3776        | 5571           | 22                  | 1.32  | (1.11–1.58)   | 3.17  | 0.002  | R     | 27.19 | 0.16 | 23.0 |
| TC vs. CC           | Overall                 | 5461        | 7742           | 22                  | 1.17  | (1.06–1.30)   | 3.06  | 0.002  | R     | 30.35 | 0.09 | 31.0 |
| TT vs. TC           | Overall                 | 2431        | 2907           | 22                  | 1.12  | (0.94–1.34)   | 1.26  | 0.21   | R     | 14.98 | 0.82 | 0.0  |
| TT+TC vs. CC        | Overall                 | 5834        | 8110           | 22                  | 1.20  | (1.08–1.34)   | 3.32  | 0.0009 | R     | 35.99 | 0.02 | 42.0 |
| TT+TC vs. CC        | Asian                   | 2713        | 2501           | 8                   | 1.13  | (0.97–1.32)   | 1.16  | 0.11   | R     | 10.55 | 0.16 | 34.0 |
| TT+TC vs. CC        | Caucasian               | 2277        | 5045           | 10                  | 1.30  | (1.09–1.55)   | 2.95  | 0.003  | R     | 17.87 | 0.04 | 50.0 |
| TT+TC vs. CC        | African                 | 844         | 564            | 4                   | 1.16  | (0.80–1.67)   | 0.77  | 0.44   | R     | 6.21  | 0.10 | 52.0 |
|                     | American                |             |                |                     |       |               |
| TT+TC vs. CC        | Atopic                  | 2198        | 2390           | 10                  | 1.25  | (1.07–1.45)   | 2.90  | 0.004  | R     | 11.60 | 0.24 | 22.0 |
| TT+TC vs. CC        | Non-atopic              | 297         | 952            | 5                   | 1.28  | (0.97–1.68)   | 1.73  | 0.08   | R     | 1.29  | 0.86 | 0.0  |
| +2044A/G            |                         |             |                |                     |       |               |
| AA vs. GG           | Overall                 | 4808        | 7055           | 31                  | 1.28  | (1.13–1.46)   | 3.81  | 0.0001 | R     | 32.41 | 0.35 | 7.0  |
| AG vs. GG           | Overall                 | 7277        | 10304          | 31                  | 1.15  | (1.06–1.25)   | 3.38  | 0.0007 | R     | 37.69 | 0.16 | 20.0 |
| AA vs. AG           | Overall                 | 4151        | 4935           | 31                  | 1.11  | (0.99–1.25)   | 1.78  | 0.08   | R     | 20.39 | 0.91 | 0.0  |
| AA+AG vs. GG        | Overall                 | 8118        | 11147          | 31                  | 1.18  | (1.08–1.28)   | 3.78  | 0.0002 | R     | 44.30 | 0.04 | 32.0 |
| AA+AG vs. GG        | Asian                   | 4770        | 5603           | 16                  | 1.19  | (1.04–1.34)   | 2.49  | 0.01   | R     | 29.20 | 0.02 | 49.0 |
| AA+AG vs. GG        | Caucasian               | 2463        | 4633           | 11                  | 1.22  | (1.06–1.40)   | 2.82  | 0.005  | R     | 13.25 | 0.21 | 25.0 |
| AA+AG vs. GG        | African                 | 781         | 408            | 3                   | 1.13  | (0.86–1.47)   | 0.88  | 0.38   | R     | 0.25  | 0.88 | 0.0  |
|                     | American                |             |                |                     |       |               |
| AA+AG vs. GG        | Atopic                  | 2486        | 2827           | 12                  | 1.12  | (1.00–1.26)   | 1.92  | 0.05   | R     | 10.60 | 0.48 | 0.0  |
| AA+AG vs. GG        | Non-atopic              | 259         | 789            | 5                   | 0.87  | (0.60–1.27)   | 0.72  | 0.47   | R     | 5.42  | 0.25 | 26.0 |

vs., versus; R, random-effects model.
Figure 3. One-way sensitivity analysis for the \textit{IL-13} $-1112\text{C}/\text{T}$ polymorphism with asthma risk.  
doi:10.1371/journal.pone.0056065.g003

Figure 4. Cumulative meta-analysis of associations between the \textit{IL-13} $-1112\text{C}/\text{T}$ polymorphism and asthma risk.  
doi:10.1371/journal.pone.0056065.g004
Figure 5. Funnel plot for asthma risk and the IL-13 $-1112C/T$ polymorphism. doi:10.1371/journal.pone.0056065.g005

Figure 6. Meta-analysis for the association between asthma risk and the IL-13 $+2044A/G$ polymorphism. doi:10.1371/journal.pone.0056065.g006
presented in Table 1. Genotype frequencies and HWE examination results are listed in Table 2.

**Quantitative Data Synthesis**

The IL-13 −1112C/T polymorphism. Twenty-two studies determined the association between \(-1112C/T\) polymorphism and asthma. The sample sizes for case and control groups were 5834 and 8110, respectively. The estimated OR1, OR2 and OR3 were 1.32 (\(P=0.002\)), 1.17 (\(P=0.002\)), and 1.12 (\(P=0.21\)) (Table 3). These estimates suggested a dominant genetic model, therefore TT and TC were combined and compared with CC. The pooled OR was 1.20 (95% CI 1.08–1.34, \(P=0.0009\)) (Figure 2). There was moderate heterogeneity (\(I^2=42\%), \(P=0.02\)). In the stratified analysis by ethnicity, a statistically significant association was found for studies with Caucasians (OR = 1.30, 95% CI 1.09–1.55, \(P=0.003\)). However, no significant association was observed in Asians and African Americans (Table 3). In the subgroup analysis by atopic status, the \(IL-13\) −1112C/T polymorphism was significantly associated with risk of atopic asthma (OR = 1.28, 95% CI 1.04–1.55, \(P=0.003\)) but not with non-atopic asthma risk (OR = 1.12, 95% CI 1.00–1.26, \(P=0.05\)). Of note, heterogeneity was significantly decreased in atopic asthma subgroup and non-atopic asthma subgroup (\(I^2=22\%), \(P=0.24\), and \(I^2=0\%), \(P=0.86\), respectively).

We conducted one-way sensitivity analysis to evaluate the stability of the meta-analysis. As shown in Figure 3, the statistical significance of the results was not altered when any single study was omitted. Cumulative meta-analyses of \(IL-13\) −1112C/T polymorphism association were also conducted. The inclination toward significant association with asthma risk was found (Figure 4). The funnel plot was seemed symmetrical (Figure 5). However, Egger’s test indicated significant publication bias (\(P=0.021\)).

**The IL-13+2044A/G polymorphism.** Thirty-one case-control studies identified an association between \(IL-13+2044A/G\) polymorphism and asthma risk. A total of 8118 cases and 11147 controls were included in this meta-analysis. The estimated OR1, OR2 and OR3 were 1.28 (\(P=0.0001\)), 1.15 (\(P=0.0007\)), and 1.11 (\(P=0.08\)), respectively (Table 3). Thus, these estimates suggested a dominant genetic model, therefore AA and AG were combined and compared with GG. The pooled OR was 1.18 (95% CI 1.08–1.28, \(P=0.0002\)) (Figure 6). Moderate heterogeneity (\(I^2=32\%), \(P=0.04\)) was found. Subgroup analysis was performed by ethnicity. Statistically significant findings were witnessed in Asians (OR = 1.19, 95% CI 1.04–1.36, \(P=0.01\)) and Caucasians (OR = 1.22, 95% CI 1.06–1.40, \(P=0.005\)) but not in African Americans. In terms of atopic status, borderline yet significant increased asthma risk was found among atopic asthma patients (OR = 1.12, 95% CI 1.00–1.26, \(P=0.05\)), but no statistically significant finding was found among non-atopic asthma patients (OR = 0.87, 95% CI 0.60–1.27, \(P=0.47\)). Again, significant decreased heterogeneity was found in atopic asthma subgroup and non-atopic asthma subgroup (\(I^2=0\%), \(P=0.48\), and \(I^2=26\%), \(P=0.25\), respectively).

In the one-way sensitivity analysis, there was little modification of the estimates after exclusion of individual study (Figure 7). Cumulative meta-analysis showed that the evidence was consistent over time (Figure 8). The shape of the funnel plots seemed symmetrical in the dominant genetic model (Figure 9). Egger’s test was used to provide statistical evidence of funnel plot symmetry. The result did not show any evidence of publication bias (\(P=0.684\)).

**Discussion**

Hallmarks of asthma include airway inflammation predominated by eosinophils, mucus hyperproduction, and airway hyperre
sponsiveness (AHR) [49]. A considerable weight of evidence supporting a role for IL-13 in asthma was derived from animal models. For instance, previous studies showed that acute administration of IL-13 itself was sufficient to recapitulate eosinophilic inflammation in nonimmunized mice or recombination-activating gene-deficient mice [50,51]. In addition, blockade of IL-13 alone in vivo through IL-13 gene targeting in mice prevented and reversed established mucus cell changes, suggesting a key role of IL-13 in mucus hyperproduction [52,53]. Furthermore, AHR can be induced by IL-13 overexpression and blockade of IL-13 by the soluble receptor-Fc fusion protein abrogated allergen-induced AHR [54]. Taken together, these results suggested that IL-13 was a critical cytokine in the development of asthma. IL-13 was one of the most studied of the candidate genes for asthma. IL-13 −1112C/T polymorphism led to increased IL-13 transcription in polarized TH2 cells and enhanced IL-13 secretion by mitogen-stimulated mononuclear cells [55]. Moreover, Arima et al. [56] indicated that the IL-13 +2044A/G polymorphism may be a functional variant. Studies demonstrated that the AA genotype resulted in decreased affinity of IL-13 for IL-13Rα2 and increased expression of IL-13 [56]. Thus, it is biologically plausible that these two polymorphisms could influence the susceptibility to asthma.

In the present meta-analysis, we explored the association between the IL-13 −1112C/T and +2044A/G polymorphisms and asthma risk, including 34 eligible case-control studies. For IL-13 −1112C/T polymorphism, 5834 cases and 8110 controls were included. We found that individuals with the −1112T allele (TT or TC) showed an increased risk of asthma in the overall population. The results from meta-analysis showed that carriers of the TT or TC genotype had 20% increased asthma risk compared to those individuals with the CC carriers. In the stratified analysis
by ethnicity, the significant association was observed in Caucasians, but not in Asians and African Americans. It is possible that different genetic backgrounds may account for these differences. However, there were only four studies using African Americans. Thus, the positive association between African Americans and asthma could not be ruled out because studies with small sample size may have insufficient statistical power to detect a slight effect. In addition, significant heterogeneity ($I^2 = 52\%$, $P = 0.10$) may also distort the result. In the subgroup analysis by atopic status, we found $IL-13 -1112C/T$ polymorphism exhibited increased atopic asthma risk. For $IL-13+2044A/G$ polymorphism, 8118 cases and 11147 controls were included. There was a significant association between this polymorphism and asthma risk. When subgroup analysis was performed according to ethnicity, significant associations were showed in Asians and Caucasians, but not in African Americans. Only three studies were performed with African Americans, thus the positive association still can not be excluded. The subgroup analysis based on atopic status found that $IL-13+2044A/G$ polymorphism was marginally associated with allergic asthma risk. Taken together, these results suggested that $IL-13$ polymorphisms may play a role in the etiology of allergic asthma.

A recent meta-analysis performed by Yang et al. [41] found $+2044A/G$ polymorphism was associated asthma risk in Asians but not in Caucasians. Another meta-analysis conducted by Cui et al. [42] showed this polymorphism was more pronounced among Caucasians but not among Asians. Results from our study were inconsistent with these meta-analyses. We found significant associations in both Asians and Caucasians. There are several potential explanations for the different results. First, different inclusion and exclusion criteria were used in these two meta-analyses [41,42]. For example, Cui et al. [42] only included English papers. However, Yang et al. [41] included articles published in English and Chinese. Thus, although these two meta-analyses were published in the same year, it was possible that different results may be observed. Second, different numbers of subjects were included in the two meta-analyses [41,42]. For $+2044A/G$ polymorphism, Cui et al. [42] included 8439 subjects in their study, while Yang et al. [41] only included 5695 subjects in their meta-analysis. Third, we noted that three studies ($n = 806$) performed using Caucasians and nine studies ($n = 4241$) performed using Asians were included in Yang’s study [41]. Moreover, six studies ($n = 4202$) conducted in Caucasians and five studies ($n = 3673$) conducted in Asians were included in Cui’s study [42]. Therefore, different statistical power might be another reason for the discrepant results. For $+2044A/G$ polymorphism, our meta-analysis included eleven case-control studies ($n = 7096$) in Caucasians and sixteen case-control studies ($n = 10373$) in Asians, thus our study was more conclusive and more powerful. Additionally, our study had some advantages. First, we attempted to find as many publications as we could by means of various searching approaches. Second, it is the first time studying the atopic specificity and $IL-13$ polymorphisms interactions. Third, the methodological issues for meta-analysis, such as, one-way sensitivity analysis and cumulative meta-analysis were well investigated.

Results from one-way sensitivity analysis and cumulative meta-analysis suggested high stability and reliability of our results. Besides, we had to mention the importance of heterogeneity and publication bias, which might influence the results of meta-analysis. In our study, moderate heterogeneity was observed for the $IL-13 -1112C/T$ and $+2044A/G$ polymorphisms. We used subgroup analysis to explore the sources of heterogeneity. After subgroup analysis by atopic status, the heterogeneity was effectively decreased and disappeared. Therefore, the main source of heterogeneity was from atopic status. Moreover, funnel plots and Egger’s tests were used to find potential publication bias. The results indicated that there was significant publication bias for $IL-13 -1112C/T$ polymorphism. Thus, our results should be interpreted with caution and more studies are still needed to evaluate the effect of $IL-13 -1112C/T$ polymorphism on asthma risk.

Several limitations need to be addressed. First, the numbers of published studies were not sufficient for a comprehensive analysis,
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Author Contributions

Financial support: QXY. Provision of study materials: WY YAL JRB BL. Collection and assembly of data: WY YAL JRB BL. Data analysis and interpretation: WY YAL JRB BL. Final approval of manuscript: WY YAL JRB BL. QXY. Conceived and designed the experiments: WY YAL JRB BL. QXY. Wrote the paper: WY YAL JRB BL. QXY.
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