Risk Factors for Chronic and Recurrent Otitis Media–A Meta-Analysis

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Abstract

Risk factors associated with chronic otitis media (COM) and recurrent otitis media (ROM) have been investigated in previous studies. The objective of this study was to integrate the findings and determine the possible risk factors for COM/ROM based on our meta-analysis. A comprehensive search of electronic bibliographic databases (PubMed, Embase, CNKI and Wanfang database) from 1964 to Dec 2012, as well as a manual search of references of articles, was performed. A total of 2971 articles were searched, and 198 full-text articles were assessed for eligibility; 24 studies were eligible for this meta-analysis. Regarding risk factors for COM/ROM, there were two to nine different studies from which the odds ratios (ORs) could be pooled. The presence of allergy or atopy increased the risk of COM/ROM (OR, 1.36; 95% CI, 1.13–1.64; P = 0.001). An upper respiratory tract infection (URTI) significantly increased the risk of COM/ROM (OR, 6.59; 95% CI, 1.31–13.89; P < 0.00001). Smoking appeared to be a significant risk factor for COM/ROM (OR, 1.96; 95% CI, 1.78–2.16; P < 0.00001). A patient history of acute otitis media (AOM)/ROM increased the risk of COM/ROM (OR, 11.13; 95% CI, 1.06–116.44; P = 0.04). Passive smoke significantly increased the risk of COM/ROM (OR, 1.39; 95% CI, 1.02–1.89; P = 0.04). Low social status appeared to be a risk factor for COM/ROM (OR, 3.82; 95% CI, 1.11–13.15; P = 0.03). Our meta-analysis identified reliable conclusions that allergy/atopy, URTI, smoking, previous history of AOM/ROM, second-hand smoke and low social status are important risk factors for COM/ROM. Other unidentified risk factors need to be identified in further studies with critical criteria.

Introduction

Chronic otitis media (COM) and recurrent otitis media (ROM) are two of the most common infectious diseases worldwide. COM and ROM affect diverse cultural and racial groups that are distributed in both developing and industrialized countries. A cross-sectional study conducted in nine countries over three continents revealed that disease prevalence is significant enough to be considered for clinical practice [1]. COM/ROM can cause hearing impairment and speech delay. COM can cause both intracranial and extracranial complications [2]. Effective treatment of the diseases depends on a thorough understanding of the risk factors.

Risk factors associated significantly with COM/ROM include ethnicity [3–5], genetic factors [6], gender [7], day-care center attendance [8], breast-feeding [9], and allergy/atopy [10] etc. as reported in previous studies. However, many of the reported studies were difficult to compare because they lacked clear case definitions, standard diagnostic criteria or control groups to evaluate the potential study biases. We conducted a meta-analysis of all available published data and qualified studies that investigated the potential risk factors for COM/ROM to clarify and propose possible means of treatment of the disease.

Materials and Methods

Study Identification

A literature search was conducted manually according to the search strategy (Text S1) to evaluate the risk factors for COM/ROM. We searched for the articles published in Pubmed, Embase, WanFang data (http://www.wanfangdata.com.cn/) and China National Knowledge infrastructure (CNKI) database (http://dlib.edu.cnki.net/kns50/). Articles from 1964 to Dec 2012 were included in the search. The search was limited to humans and performed with no language restrictions. Reference lists of the relevant original and reviewed articles were evaluated to identify additional studies. We used controlled vocabularies (Explosion mapped searches of MeSH terms or Emtree thesaurus terms) and text words for chronic otitis media, recurrent otitis media, middle ear cholesteatoma, and mastoiditis. Concepts related to “Otitis media” with the subheadings of congenital, epidemiology, genetics, immunology, microbiology and virology for all Mesh terms in PubMed were reviewed. Areas of focus that were chosen for otitis media in Embase were genetics, immunology and hematol, microbiology, otorhinolaryngology, pediatrics and public health. Furthermore, terms indicating risks, such as “risk factors”, “probability”, “odds ratio”, “risk assessment”, “causality”, “epidemiologic factors”, “epidemiology”, “epidemiologic
studies”, “multivariate analysis”, “logistic models” and their entry terms were also included (see Text S1). Overall, 2547 papers were retrieved from Pubmed, 479 papers were retrieved from Embase, 116 papers were retrieved from CNKI and 10 were retrieved from Wanfang. A total of 151 additional records were retrieved from the manual reference search of the related articles. The workflow of this study follows guidelines by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [11](Figure 1).

Definition of COM/ROM

The diagnosis criteria of COM/ROM was described in individual studies, which included case history, physical examination and other examinations such as tympanogram, microscopic otoscopy or tympanostomy tube insertions (Table 1). The abbreviation COM includes the types of chronic suppurative otitis media (CSOM) and chronic otitis media with effusion (COME). Chronic otitis media with cholesteatoma was not excluded from the COM definition, although no study involving that type was eligible for our meta-analysis.

Study Selection and Quality

We included the study of the prospective cohort, case-cohort, and nested case-control design, case control or nested case-control, retrospective case-control, and cross-sectional studies. The publications included were required to meet the following criteria:

1. Inclusion of human subjects
2. Clear definitions of COM/ROM and estimation of the association of the relative risks (hazard ration, risk factors) of COM/ROM;
3. The numbers for both controls and COM/ROM cases;
4. Sufficient data are to determine the odds ratio (OR) with 95% confidence intervals (CIs).

Figure 1 PRISMA Flow Diagram.
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Table 1. Characteristics of included studies.

| First author | Year of publication | Risk factor | Type of otitis media | Study type | Age, years of participants | Study duration | Number of cases | Number of controls | Total Sample Size | Study Location | Ethnic Group | Diagnostic criteria of COM/ROM |
|--------------|---------------------|-------------|----------------------|------------|---------------------------|---------------|-----------------|-------------------|-----------------|----------------|-------------|--------------------------------|
| Stahlberg, M. R. [37] | 1986 | Day-care center attendance, Passive smoke, Low socioeconomic status | ROM | Case-control | 10–44 months in case group, 14–38 months in control group | March, 1983–Feb, 1984 | 115 | 222 | 337 | Turku, Finland | Inhabitants in Turku, Finland | Three or more episodes of OME |
| Daly, K. [8] | 1988 | Sex, Day-care center attendance, White people, Allergy, Family history of OM | COME | Case-control | 10 months -8 years of age | Jan, 1982-Sep, 1984 | 177 | 182 | 359 | Minnesota, USA | White people and others unidentified population | MEE persisted in one or both ears at the 3- and 6 week visits, or AOM without resolution of MEE during the 6 weeks |
| Fliss, D. M. [21] | 1991 | History of AOM/ROM, Day-care center attendance, Larger families and more siblings, Sex, Allergy, Sinusitis and recurrent URTI, Breast feeding, Passive smoke | CSOM without Cholesteotoma | Case-control | 2–15 years of age | Jan, 1987-April, 1990 | 88 | 76 | 164 | Southern Israel | Jewish population | Chronic or recurrent mucous middle ear secretion persisting for at least 6 years. |
| Kalm, O. [27] | 1994 | HLA frequency | CSOM | Follow-up | Mean age 16.4 | Follow up 11.1 years | 40 | 1701 for HLA-A and B 438 for HLA-C 102 for HLA-DR | 1741 | Sweden | No comment | Chronic or recurrent mucous middle ear secretion persisting for at least 6 years. |
| Kvaerner, K. J. [29] | 1996 | Birth weight, Gestational age | ROM | Case-control | Before age 7 | Baby born between 1967–1974 | 519 | 5345 | 5864 | Norway | Norwegian twin pairs | Recurrent ear infections |
| Ilicali, O. C. [24] | 1999 | Passive smoke, Sex | ROM | Follow-up | 3–7 years of age | May 1st, 1995–Nov 30th, 1996 | 166 | 166 | 332 | Istanbul, Turkey | Patients from Istanbul School of Medicine | Extensive OM bilateral for at least 3 months or 6 months unilateral, 3 episodes of AOM during previous 6 months or minimum 4 episodes during previous 1 year. |
| Junntti, H. [26] | 1999 | Cow's milk allergy | ROM | Case control | 9–11 years of age. Mean age = 10.5 ± 0.6 years | 1986–1987 | 56 | 204 | 260 | Finland | Local residents | 15 episodes of OM in 10 years |
| Engel, J. [19] | 2001 | Sex, Gestational age, Birth weight | COME | Prospective cohort | 2 years of age | 2-year follow-up | 43 | 40 | 83 | Netherland | Newborns from Maastricht University Hospital | Otoscopy and tympanometry examination to assessed combined with MOMES diagnostic-algorithm |
| First author | Year of publication | Risk factor | Type of otitis media | Study type | Age, years of participants | Study duration | Number of cases | Number of controls | Total Sample Size | Study Location | Ethnic Group | Diagnostic criteria of COM/ROM |
|--------------|---------------------|-------------|----------------------|------------|---------------------------|---------------|----------------|------------------|-----------------|---------------|--------------|--------------------------------|
| Ilicali, O. C. [23] | 2001 | Passive smoke | ROM | Follow-up | 3–8 years of age | Oct, 1996–Apr, 1998 | 114 | 40 | 154 | Istanbul, Turkey | Local residents | ONE persisted for ≥3 months bilateral or ≥6 months unilateral. ≥3 episodes of ROM during previous 6 months or ≥4 episodes during the previous year. |
| Ramet, M. [33] | 2001 | Surfactant protein-A frequencies | ROM | Case-control | 1–10 years of age, mean age = 8.4±5.2 | No comment | 147 | 228 | 375 | Finland | Local patients and residents | At least 5 episodes of AOM |
| Daly, K. A. [17] | 2004 | Support for linkage at chromosomes 10q and 19q, Day-care center attendance, Exclusively formula fed, Passive smoke | COME/ROM | Retrospective cohort | Family members, age not mentioned | 1992–2001 | 371 | 245 | 616 | Minnesota, USA | Families recruited from University of Minnesota | Tymanostomy tube surgery for COME/ROM |
| Keles, B. [28] | 2004 | Pharyngeal reflux, Gastroesophageal reflux | COME | Prospective cohort | 3–7 years, mean age = 6±3.1 | No comment | 25 | 12 | 37 | Konya, Turkey | No comment | COME ≥3 months |
| Engel, J. A. [20] | 2005 | Breast feeding, Day-care center attendance, Family history of OM, Passive smoke, Snoring, URTI, Mother's smoking during pregnancy, Medication use during pregnancy | ROM | Prospective cohort | 2.1–7.5 years of age | Dec, 1999–Aug, 2003 | 73 | 17 | 90 | Nijmegen and Winterswijk, Netherlands | No comment | MEE at least for 3 months |
| Chantry, C. J. [16] | 2006 | Breast feeding | ROM | Prospective cohort | 6–72 months of age | 1988–1994 | 88 | 271 | 359 | USA | White, black, Mexican American | ≥3 episodes of OM |
| Gozal, D. [22] | 2008 | Snoring, African American, Chronic nasal obstruction, Allergy, Passive smoke | ROM | Retrospective cohort | 5–7 years of age | 1999–2004 | 5074 | 11247 | 16321 | Louisville, USA | African American and other unclassified ethnic groups | History of ROM and insertion of tympanostomy tubes |
| Lasisi, A. O. [30] | 2009 | Serum retinol level | CSOM | Follow-up | 6 months–7 years, mean age = 7.8 years | No comment | 116 | 52 | 168 | Ibadan, Nigeria | No comment | Persistence of otorrhoea ≥3 months |
| Lasisi, A. O. [31] | 2007 | URTI, Indoor-cooking, Allergy, Low social status group, Passive smoke, Breast-feeding, Day-care center attendance | COME | Case-Control | 30 days–14 years of age | No comment | 189 | 100 | 289 | Nigeria | No comment | ≥3 episodes of OM in 1 year |
| First author       | Year of publication | Risk factor                                      | Type of otitis media | Study type           | Age, years of participants | Study duration     | Number of cases | Number of controls | Total Sample Size | Study Location | Ethnic Group | Diagnostic criteria of COM/ROM |
|--------------------|---------------------|--------------------------------------------------|----------------------|----------------------|---------------------------|-------------------|-----------------|------------------|------------------|----------------|--------------|--------------------------------|
| Schejbel, L [36]   | 2009                | Properdin deficiency                             | ROM                  | Retrospective cohort | All age from three generations of a family | No comment | 4               | 21               | 25               | Denmark         | Indian       | Several episodes of OM          |
| Bakhshaee, M. [15] | 2011                | Allergy                                          | CSOM                 | Prospective cohort   | 10–50 years, mean age = 30 years | No comment | 68              | 184              | 252              | Mashad, Iran    | No comment | CSOM diagnosed for at least 1 year |
| Elemraid, M. A. [18]| 2011                | Nutritional factors                               | CSOM                 | Case-control study   | 0.6–15 years (mean = 6.0) in case group 0.9–15 years (mean = 8.2) in control group | March to May 2007 | 75              | 74               | 149              | Sana’a, Yemen  | Local children | Diagnosis of CSOM and history of persistent discharging ear(s) for at least 2 weeks |
| Jensen, R. G. [25]| 2011                | Sex, Ethnicity, Low education of mother, Family history of COM, Breast feeding | CSOM                 | Follow-up            | 11–15 years               | 1996–2008 | 45              | 191              | 236              | Nuuk and Sisimiut, Greenland | Inuit, Danish, Mixed | ≥2 weeks of otorrhoea for ≥3 months |
| Nelson, H. M. [32]| 2011                | Overweight in toddlers                            | ROM                  | Prospective cohort   | 1 month-27 months. Mean age = 24.1 months | 1991–1996 | 203             | 227              | 430              | Minneapolis, USA | Local toddlers | ROM treated with tympanostomy tubes |
| Sale, M. M. [35]   | 2011                | Day-care center attendance, Breast feeding, Allergy | COME/ROM             | Case-Control         | Mean age = 5.9 in case group. 5.4 in control group | Oct, 1996 - Apr, 1998 | 380             | 238              | 618              | Istanbul, Turkey | Local residents | OME or ROM treated with ventilation tubes |

Abbreviation: OM: Otitis media. OME: Otitis media with effusion. URTI: upper respiratory tract infection. CSOM: Chronic suppurative otitis media. COME: Chronic otitis media with effusion. MEE: Middle ear effusion. ROM: Recurrent otitis media. RAOM: Recurrent acute otitis media. MOMET: Maastricht Otitis Media with Effusion Study. TM: Tympanic membrane.

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We excluded descriptive studies, case reports, case series, reviews, letters, commentaries, and studies on the pathogenesis and treatment of COM/ROM. We excluded repeated reports with a small number of participants and these data were included in large studies mentioned above. We excluded the studies of recurrent acute otitis media, congenital cholesteatoma and unclassified OM. Inclusion discrepancy was resolved in joint discussions by the investigators. We appraised the quality of the studies, focusing on the selection of cohorts and assessment of the outcomes.

Data Extraction

Two investigators, (Yan Zhang and Jin Zhang) independently extracted and registered the data from the eligible publications. The following data from each article was extracted: author, year of publication, risk factor, type of otitis media, study type, age/years of participants, study duration, number of cases, number of controls, total sample size, study location, ethnic group and treatment of COM/ROM. We excluded descriptive studies, studies on pathogenesis, pathologies, and treatment, and microbiological studies. A total of 103 case control or cohort studies examined the risk factors of COM/ROM, and 79 studies failed to meet the inclusion criteria for the following reasons: unclear definition of COM/ROM, no classification of OM, no control groups, and inadequate data for abstraction. For repeated studies, we retained the one with the larger sample size. Figure 1 shows the selection flow for this meta-analysis; 24 independent studies met all of the inclusion criteria [8,15–38]. The characteristics of the included studies are summarized in Table 1.

### Statistical Analysis

The meta-analysis was processed using Review Manager 5.1, version: 5.1.6. We estimated the odds ratios (ORs) and 95% confidence intervals (CIs), and the statistical heterogeneity of the studies was assessed after combining the results. Estimates of the risk factors were pooled using a random effects model [12]. Inconsistency of the studies was quantified by using the I² statistic, which describes heterogeneity across studies. I² values of <25% and >50% reflects low and high heterogeneity, respectively [13]. A sensitivity analysis was performed by calculating the outcomes after a single study was omitted in each turn. Finally, publication bias was assessed by performing funnel plots [14] (see Figure S1).

### Results

#### Literature Search and Study Selection

Of the total 2971 relevant references identified, 198 articles were considered potentially relevant. The excluded references that were considered irrelevant included reviews, letters, commentaries, studies on pathogenesis, pathologies, and treatment, and microbiological studies. A total of 103 case control or cohort studies examined the risk factors of COM/ROM, and 79 studies failed to meet the inclusion criteria for the following reasons: unclear definition of COM/ROM, no classification of OM, no control groups, and inadequate data for abstraction. For repeated studies, we retained the one with the larger sample size. Figure 1 shows the selection flow for this meta-analysis; 24 independent studies met all of the inclusion criteria [8,15–38]. The characteristics of the included studies are summarized in Table 1.

#### Pooled Analysis of Risk Factors

Pooled data from 7 studies indicated the presence of allergy or atopy and increased the risk of COM/ROM (OR, 1.36; 95% CI, 1.13–1.64; P=0.001). A total of four studies investigated the association between upper respiratory tract infection (URTI) and COM/ROM, which includes the presence of cough or rhinorrhea or nasal stuffiness or sore throat or adenoiditis/adenoid hypertrophy. Pooled data from these showed that URTI significantly increased the risk of COM/ROM (OR, 6.59; 95% CI, 3.13–13.89; P<0.00001). A total of two studies showed that snoring appeared to be a significant risk factor for COM/ROM (OR, 1.96; 95% CI, 1.78–2.16; P<0.00001). Pooled data from two studies revealed that a patient history of AOM/ROM increased the risk of COM/ROM (OR, 11.13; 95% CI, 1.06–116.44; P=0.04); nine studies investigated parental smoking, exposure to smoking at home and other smokers residing in the same household of frequent visitors. Pooled data showed Second-hand smoke, including the conditions above, increased the risk of COM/ROM (OR, 1.39; 95% CI, 1.02–1.89 P=0.04). Pooled

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**Table 2. Pooled analysis of risk factors.**

| Risk factor                          | No. of studies/references | No. of subjects | OR     | 95% CI          | P value | I² (%) |
|-------------------------------------|---------------------------|-----------------|--------|-----------------|---------|--------|
| Allergy/Atopy                        | 7 [8,15,21,22,26,31,35]   | 18263           | 1.36   | [1.13, 1.64]    | 0.001   | 26     |
| Upper respiratory tract infections   | 4 [20,21,31,38]           | 865             | 6.59   | [3.13, 13.89]   | <0.00001| 65     |
| Chronic nasal obstruction            | 2 [22,31]                 | 16610           | 1.19   | [0.84, 1.69]    | 0.34    | 54     |
| Snoring                             | 2 [20,22]                 | 16411           | 1.96   | [1.78, 2.16]    | <0.00001| 0      |
| Sex (male)                          | 6 [8,19,21,24,25,38]      | 1435            | 1.24   | [0.99, 1.54]    | 0.06    | 0      |
| Attending day-care centers           | 7 [8,17,20,21,31,35,37]   | 2454            | 1.70   | [0.95, 3.05]    | 0.07    | 89     |
| Family history of otitis media       | 4 [8,19,25,38]            | 1166            | 1.40   | [0.86, 2.28]    | 0.18    | 52     |
| Patient history of AOM/ROM           | 2 [21,38]                 | 425             | 11.13  | [1.06,116.44]   | 0.04    | 94     |
| Passive Smoke                       | 9[17,20–24,31,37,38]      | 18876           | 1.39   | [1.02, 1.89]    | 0.04    | 80     |
| Low social status group              | 2 [31,37]                 | 600             | 3.82   | [1.11, 13.15]   | 0.03    | 82     |
| Low education level of mother        | 2 [25,38]                 | 495             | 1.68   | [0.32, 8.88]    | 0.54    | 90     |
| Mother’s smoking during pregnancy   | 2 [20,24]                 | 422             | 2.34   | [0.64, 8.54]    | 0.20    | 70     |
| Larger families and more siblings    | 2 [21,38]                 | 425             | 1.57   | [0.93, 2.63]    | 0.09    | 5      |
| Breast feeding ≥6 months             | 2 [16,25]                 | 912             | 0.57   | [0.17, 1.93]    | 0.36    | 88     |
| Breast feeding (yes/no)              | 3 [17,21,35]              | 1363            | 0.91   | [0.47, 1.79]    | 0.79    | 86     |

OR: Odds ratio. 95% CI: 95% confidence intervals. I² describes heterogeneity across studies.

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data from two studies showed low social status as an increased risk factor of COM/ROM (OR, 3.82; 95% CI, 1.11–13.15; P = 0.03).

The factors that were determined to not be significantly associated with increased risk included chronic nasal obstruction (OR, 1.19; 95% CI, 0.84–1.69; P = 0.34), male sex (OR, 1.24; 95% CI, 0.99–1.54; P = 0.06), attending day-care centers (OR, 1.70; 95% CI, 0.95–3.05; P = 0.07), family history of otitis media (OR, 1.46; 95% CI, 0.96–2.28; P = 0.10), low education of the mother (OR, 1.68; 95% CI, 0.92–3.0; P = 0.05), mother’s smoking during pregnancy (OR, 2.34; 95% CI, 1.64–5.4; P = 0.20), larger families and more siblings (OR, 1.57; 95% CI, 0.93–2.63; P = 0.09). Pooled data revealed that an association between breast-feeding >6 months and COM/ROM was not statistically significant (OR, 0.57; 95% CI, 0.17–1.93; P = 0.36), neither was an association between breast feeding (yes/no) and COM/ROM (OR, 0.91; 95% CI, 0.47–1.79; P = 0.79). Pooled risk factors for COM/ROM are summarized in Table 2 and Figure S2.

Other risk factor investigations for COM/ROM included in our eligible studies included HLA frequencies [27], nutritional factors [18], medication use during pregnancy [20], ethnicities of Greenland [25], White [8], African American [22], properdin deficiency [36], indoor cooking [31], pharyngeal reflux [28], overweight status [32], older siblings [38], dietary history [18], serum retinol [30], genome scan for loci of 10q and 19q [17], and?Surfactant protein-A gene locus [33]. Unfortunately, only one research group reported each risk factor above, which made the data unavailable. There was an association between gestational age and COM/ROM from two research groups [19,29], but birth weight and COM/ROM from these groups applied different criteria and made it impossible to combine the data.

**Discussion**

COM/ROM is a disease with different possible etiologies. Using a meta-analysis design applying strict diagnostic and inclusion criteria, we performed a reliable study to investigate the risk factors associated with the disease. This study is to the best of our knowledge the first meta-analysis investigating the risk factors for COM/ROM. There are two published studies on the risk factors and etiology of AOM [39,40].

Allergy or atopy is a significant risk factor for COM/ROM. Indoor allergens and respiratory allergies such as allergic rhinitis contribute to the onset of COM/ROM. The prevalence of atopic conditions, including allergic rhinitis in patients with COM/ROM ranges from 24% to 89% [41]. New evidence from cellular biology and immunology explained allergy as a cause for Eustachian tube (ET) obstruction [42]. People with allergic or atopic conditions are more likely to suffer from COM/ROM.

Upper respiratory tract infection (URTI), which includes the presence of cough or rhinorrhea or sore throat, was indicated as a significant prognostic factor for COM/ROM. Studies support that the mucosal condition of ET could be affected by URTI [43]. A preceding or concurrent viral URTI, as well as a poly-microbial disease is considered one of the risk factors for the onset of OM. Viral URTI promotes the replication of the bacterial infection and increases inflammation in the nasopharynx and ET [44].

Snoring, defined as the presence of loud snoring at least three times per week, is a common symptom in children and is highly prevalent in children [45]. Eligible studies in this meta-analysis suggested that the risk for COM/ROM appeared to be related to the presence of snoring. Snoring is pathophysiologically determined by the size of the upper airway lymphadenoid tissue size [46]. The mechanism underlying snoring and COM/ROM appears to be increasing upper airway resistance as well as Eustachian tube dysfunction [22]. Early evaluation and intervention in children with loud snoring may prevent them from developing middle ear disease.

Previous history of AOM/ROM was studied as a predictive factor for COM/ROM. Subjects who experience episodes of AOM/ROM have an increased risk of developing chronic and recurrent middle ear infections.

Second-hand smoke has been reported to be associated with increased prevalence of middle ear disease [47]. In the meta-analysis of risk factors for acute otitis media, it was concluded that parental smoking increased the onset of acute middle ear infectious disease in children [39]. Our study drew the same conclusion about Second-hand smoking as a remarkable causative factor that contributes to the morbidity of COM/ROM. Several studies suggest that nicotine and other smoking products could make subjects more susceptible to ear infections and enhance the possibility of microorganism invasion to the middle ear. Smoke exposure could impair the mucociliary function of the ET, resulting in blockage of the nasopharyngeal airway [48]. Microorganism adherence to the epithelial cell surface and depression of local immune function were both investigated as the pathogenetic mechanism of the onset of middle ear disease caused by Second-hand smoking [49]. Effective methods should be urgently taken to decrease the prevalence of the smoke exposure.

The possibility that COM/ROM is associated with low social status has been debated for a long period of time [50]. Our data from two eligible studies considered the social prestige of professions and occupations, as well as income earnings of the parents. The statistical data revealed that patients with COM/ROM were more often belonged to low socioeconomic conditions than the controls. Various reports concerning this hazard originated from poor housing, environmental and occupational conditions [31,52].

Sex difference in otitis media risk has been estimated in various studies. Other than a conclusion that the male sex was more likely to suffer from acute otitis media in children [39], our study failed to find any significance in the difference between male and female morbidity of COM/ROM.

Breast-feeding is believed to provide antimicrobial, anti-inflammatory, and immunomodulatory agents that contribute to an optimal immune system [53]. The relative contribution of breast-feeding to preventing middle ear infection otitis media risk has been reported in numerous studies [54–56]. It is reported that breast-feeding, even for only 3 months, could decrease the risk for acute otitis media in children [39]. However, patients with COM/ROM did not differ from the control group in this respect in our study. The study for preventative effects of breast-feeding over 6 months failed to find statistical significance within the control group. Even without any breast-feeding, the impact on the incidence of COM/ROM appeared to be unremarkable in our meta-analysis.

Day-care center attendance could increase the risk of children’s exposure to respiratory pathogens. It has been reported to be a significant risk factor for acute respiratory infectious disease in children [39,52,57]. However, this was not consistent with some other studies [50]. In this meta-analysis, no association was found between COM/ROM and day-care center attendance.

The causal relationship between other factors, which include chronic nasal obstruction, family history of otitis media, mother’s smoking during pregnancy and COM/ROM is not completely established. Association between larger families and more siblings with COM/ROM was not statistically significant.
Genetic predisposition is considered to be an important prognostic factor that could influence the risk of otitis media. Previous candidate gene studies associated a number of immune system genes with otitis media, which included TNF-α, IL-6, IL-10, Tlr4, surfactant, CD14, FcγRIIa, IFNγ, Eya4, p73, MyD88, Fas, E2F4, Plg, Fbxo11, and Evx1 [59]. Other genetic predispositions include HLA frequencies and properdin deficiency. Unfortunately, eligible studies included in our meta-analysis investigated single gene defects in each study, which made it impossible to pool the data and make a conclusion.

Similar to risk factors for genetic predisposition, other risk factors for COM/ROM prevented the data from being pooled in our eligible studies; these include nutritional factors, medication use during pregnancy, ethnicities of Greenland, White, African American, indoor cooking, pharyngeal reflux, and overweight status.

The association between gestational age and COM/ROM from the two groups [19,29], birth weight and COM/ROM from the same groups applied different criteria and thus made it impossible to combine the data.

We noticed that the risk factors of sex, attending day-care centers, large families and more siblings have p-values of 0.06, 0.07 and 0.09, respectively. With the application of the 0.05 p-value, which is the conventionally used criterion, no significance was found. Using a cut-off of 10% for significance may ameliorate this problem but could increase the risk of drawing a false positive conclusion (type I error) [13,60]. However, these three risk factors should be at least considered as constituting a strong trend of risk factors for COM/ROM.

In judging the inconsistency of the studies, $I^2$ was applied to test heterogeneity. In our studies of no inconsistency ($I^2 = 0$) or low heterogeneity ($I^2<25\%$), using either fixed or random effect models produced identical results and the same direction of effect. The random effect model was the standard approach for the studies of moderate to high $I^2$ values. Some analysts might try to reduce the heterogeneity by limiting the meta-analysis to smaller more homogeneous study group. However, this could probably result in misleading conclusions if not performed with care or may limit the scope of the meta-analysis and essentially eliminates any useful information [61]. The random effect model, which was the available model to incorporate and evaluate sources of heterogeneity [12], was applied in our study. In our meta-analysis, a limited number of included studies confined our attempts to divide the studies into subgroups. Sources of between-study heterogeneity could probably originate from different study designs, sample size in each individual study, incidence rates among unexposed, length of follow-up, and/or study qualities. In our sensitivity analysis, the observed directions and magnitudes of effects weren’t changed significantly after a single study was randomly omitted in each turn.

A full understanding of the etiologic factors for COM/ROM could be beneficial for the treatment and prevention of the disease. Our study evaluates the risk factors by an objective scientific procedure, meta-analysis, to provide precise causal prophylaxis evidence. Meta-analysis is widely used in medical studies of randomized clinical trials, as well as etiologic factors of the disease. The controversy of meta-analysis is in the homogeneity of the studies. Dickersin and others noted that heterogeneity is not all that had [62,63]. It improves the generalizability of the meta-analysis results. The pooled estimates of odds ratios are valuable and important indicators for assessing the risk factors of a disease. The heterogeneity of risk factors is carefully estimated, and the results are cautiously interpreted in our study.

Conclusions

The risk factors for COM/ROM are closely interrelated. Our meta-analysis identified reliable conclusions that allergy/atopy, upper respiratory tract infection, snoring, previous history of AOM/ROM, Second-hand smoke, low social status are important risk factors for COM/ROM. Other unidentified risk factors investigated in single studies need possible repeated studies with critical criteria to be estimated properly. We suggest that the above COM/ROM risk factors be interfered effectively to prevent and decrease the onset of the disease.

Supporting Information

Figure S1 Funnel plot. Symmetric inverted funnel shape indicates unlikely publication bias. (TIFF)

Figure S2 Risk factors for COM/ROM. Pooled odds ratios from eligible studies analyzed in the meta-analysis of risk factors for COM/ROM (TIFF)

Checklist S1 PRISMA checklist. (DOC)

Text S1 Search strategy. (DOC)

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Author Contributions

Conceived and designed the experiments: YZ, MX. Performed the experiments: YZ, JZ. Analyzed the data: YZ, LXZ, YFW. Contributed reagents/materials/analysis tools: YZ, QYZ, YFW. Wrote the paper: YZ, QYZ.
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