Original Article

Bacterial lysate add-on therapy in adult and childhood asthma: a systematic review and meta-analysis

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Background: It has been proposed that bacterial lysates may serve as a suitable immunomodulatory oral medication to improve and control asthma symptoms. However, the difference in its efficacy in adults and children remains unclear.

Methods: Randomized controlled trials (RCTs) evaluating OM-85 add-on therapy in asthma patients up to December 2021 were searched using PubMed, Scopus, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang database, and WP (WeiPu) database. Risk of bias was evaluated using the Cochrane risk of bias assessment tool.

Results: A total of 36 studies were included. The results showed that OM-85 add-on treatment provided a 24% improvement in asthma symptom control [relative rates (RR) =1.24, 95% confidence intervals (CI): 1.19–1.30], and also significantly improved lung function, increased numbers of T-lymphocytes and the subtypes, and elevated levels of interferon-γ (IFN-γ), interleukin-10 (IL-10), and IL-12. Levels of serum immunoglobulin E (IgE), eosinophil cationic protein (ECP) and pro-inflammatory cytokines (including IL-4 and IL-5) were suppressed in the OM-85 add-on treatment group. Moreover, OM-85 add-on treatment showed more prominent effects in asthmatic children than in asthmatic adults.

Conclusions: OM-85 add-on therapy showed important clinical benefits for patients with asthma, especially asthmatic children. Further studies focusing on the immunomodulatory function of OM-85 in personalized asthma treatment are warranted.

Keywords: Asthma; bacterial lysates; clinical symptoms; immunotherapy

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Introduction

The hygiene hypothesis suggests that reduced exposure to microorganisms in early life leads to an increased incidence of allergic diseases. The early life period is crucial to the establishment of immune tolerance, which is important for the maintenance of stable and normal physiologic functioning of the innate and adaptive immune responses (1). A balanced and stable immune function of the airway relies on appropriate interactions between the microbiota colonizing the mucosa, host immune responses, and

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environmental microorganisms (2).

Increased urbanization has considerably improved hygiene status and altered daily life patterns. Increased rates of caesarean section, reduced rates of breastfeeding, and overuse of antibiotics may considerably decrease microorganism diversity, which contributes to dysfunctional immune tolerance and promotes the occurrence of allergic diseases such as asthma. Based on these theoretical backgrounds, the influence of environmental microbial components on functions of the immune system has been garnering increasing attention. Subsequently, numerous animal and clinical trials have been used to examine microorganisms and their lysates or metabolites.

OM-85 (Broncho-Vaxom) has been widely used as an immunomodulator since the 1950s. OM-85 is a low endotoxin alkaline lysate, prepared using a standardized process from 21 strains of five bacterial genera (including Moraxella, Hemophilus, Klebsiella, Staphylococcus, and Streptococcus) that colonize the human respiratory tract (3). Currently, OM-85 is normally used in clinical treatment to prevent recurrent respiratory tract infections. Because atopic individuals tend to develop respiratory infections due to unbalanced T helper-1 (Th1) and T helper-1 (Th2) immune responses (4), strengthening the airway anti-pathogenic function is considered an important strategy in the treatment of patients with allergic diseases.

Orally administered OM-85 has been shown to decrease alveolar inflammatory cell infiltration in various murine models of allergic airway inflammation by reducing the levels of Th2 cytokines and promoting the proliferation of regulatory T cells (5-8). OM-85 has also been empirically used by numerous pediatricians to control or relieve wheezing symptoms in pediatric patients. However, whether OM-85 actually shows clinical benefits in alleviating asthma symptoms in patients remains controversial. In this study, we used a meta-analysis to determine whether OM-85 is beneficial in alleviating the clinical symptoms of asthma, and to compare differences in the efficacy of treatment using OM-85 in adults and children with asthma. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1469/rc).

Highlight box

Key findings

- OM-85 add-on therapy showed important clinical benefits for patients with asthma, especially asthmatic children.

What is known and what is new?

- OM-85 could significantly improve asthmatic symptoms, decrease the number of asthma exacerbations, and reduce airway dysfunction. Besides, OM-85 treatment showed immune-modulatory effects by increasing the level of immunoglobulins and the number of T-lymphocyte and its subsets and related cytokines.
- Our subgroup analysis supported a more prominent effect of OM-85 on asthmatic children compared to adults.

What is the implication, and what should change now?

- OM-85 add-on therapy show promising effects on asthma treatment. Our results provided convincing evidence supporting a potential application of OM-85 in asthma treatment strategy, especially for asthmatic children with recurrent airway infections and poor disease control.

Methods

Search strategy and selection criteria

We conducted a systematic literature search of PubMed, Scopus, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang database, and WP (WeiPu) database. The search used the following keywords: "bacterial lysate", "bacterial extract", "OM-85", and "asthma". There were no language or time restrictions imposed on the search. All identified literature was entered into Endnote. After removing duplicate articles using Endnote, the following outcomes were excluded first: review and meta-analyses, case reports, editorials, preprints, communications and letters, data articles, notes, commentaries, news, brief surveys, errata and retractions, guidelines, and mathematical models. To determine the eligibility of the articles, two reviewers screened the included literature using the following three steps. First, the title of the article was examined. Then, the abstract of the article was examined. Finally, the subject and targeted disease of the article were identified by evaluating the full text of the article. Any disagreement was resolved by discussion with a third reviewer to reach consensus. Articles with computable data obtained from clinical examinations relevant to asthma (such as those of lung function, serum T-lymphocyte subsets, serum cytokine levels, and serum and induced sputum immunoglobulin levels) were included in the current meta-analysis. The study registration number is CRD42022322815, and its registration name is "*A systematic review and meta-analysis of the bacterial lysate treatment in adults and children asthma*."

For inclusion in this review, studies had to meet all of the following criteria: (I) study design: randomized controlled

trials without language restriction; (II) participants: children and adults diagnosed with any type of asthma; (III) intervention group: patients who received at least one course of OM-85 alone, or OM-85 combined with conventional symptomatic treatment of asthma; (IV) control group: asthma conventional therapy group or placebo alone group; (V) outcome assessment: each study had to provide data on valid or invalid laboratory tests. Exclusion criteria were as follows: (I) study was not a randomized controlled trial; (II) no primary outcome data were available; (III) trials using bacterial lysates other than OM-85; (IV) studies on the intervention of OM-85 in mice.

Data collection

Data were extracted independently by two reviewers. Any disagreement was resolved by discussion or by consulting the third reviewer until consensus was reached. The extracted data included the following information: authors of the study, year of the study, country in which the study was performed, language of the study, study design, sample size (intervention group/control group), groups, adverse events, primary outcomes [including frequency of asthma exacerbation, efficacy of intervention treatment, and predicted Forced expiratory volume in 1 second (FEV_1%)], secondary outcomes [including serum immunoglobulin (IgG, IgM, IgE, or IgA) levels, total serum eosinophil (EOS) count, eosinophilic cationic protein levels, sputum sIgA levels, and proportion of T lymphocyte subtypes ($CD3^+$, $CD4^+$, $CD8^+$ or $CD4^+/CD8^+$). For meta-analysis, the format of laboratory values, presented as median [interquartile range (IQR)], was transformed into mean [standard deviation (SD)]. Data were pooled whenever two or more publications reported a given parameter. If both adults and children were included in a study conducted to analyze a given outcome, adults and children were divided into two subgroups for analysis.

Statistical analysis

In meta-analysis, dichotomous data are presented as relative rates (RRs) with 95% confidence intervals (CI). Continuous data are presented as standard mean differences (SMDs) with 95% CI. When both adults and children were included in studies evaluated in our analysis, subgroup analysis was performed according to age (patients under 14 years old were defined as children, and patients over 18 years old were defined as adults). The I^2 statistic was used to assess heterogeneity. Heterogeneity was considered low if I^2 was between 25–50%. I^2 values between 50% and 75%, and 75% and 100%, indicated moderate and high heterogeneity, respectively. I^2 values below 25% indicated no heterogeneity. All analyses were performed using Stata se-64. Risk of bias was assessed using the Cochrane risk of bias assessment tool.

Results

Study characteristics

A total of 731 records were identified using database searching. Of these 731 records, 614 records were selected for further assessment. We also assessed 319 full-text reports for inclusion in this meta-analysis. *Figure 1* shows a PRISMA flow diagram of our search and eligibility results. We excluded 225 publications mainly because of ineligible study design or lack of patient laboratory data. Finally, 36 eligible publications were included in this review. Of these 36 eligible publications, 33 were published in Chinese and 3 in English. Another Chinese articles did not record the specific number of asthma attacks, nor did data from other laboratory tests, only data related to adverse effects was used for meta-analysis (9). A total of 3,030 patients were enrolled in this study; of these patients, the OM-85-treated group contained 1,551 participants, while the control group contained 1,479 participants. Nineteen studies reported on the rate of symptom improvement and nine studies reported on the frequency of asthma exacerbations. Seventeen and 15 studies analyzed changes in lung function and T lymphocyte subsets, respectively. Sixteen studies reported on immunoglobulin levels in serum or induced sputum, and 7 studies described changes in EOS numbers or ECP levels in serum. Eighteen studies reported on changes in serum cytokine levels in asthma patients. Seventeen trials investigated the adverse effects of OM-85. A total of 31 articles reported on findings obtained in children, and the remaining five studies reported on findings obtained in adults. The essential characteristics of the included studies are presented in *Table 1*.

Assessing the risk of bias in included trials

In all the major included studies, the outcome of asthma-related clinical symptoms was assessed using a questionnaire. In some of the studies, description of methodology used for the selection and allocation of trial

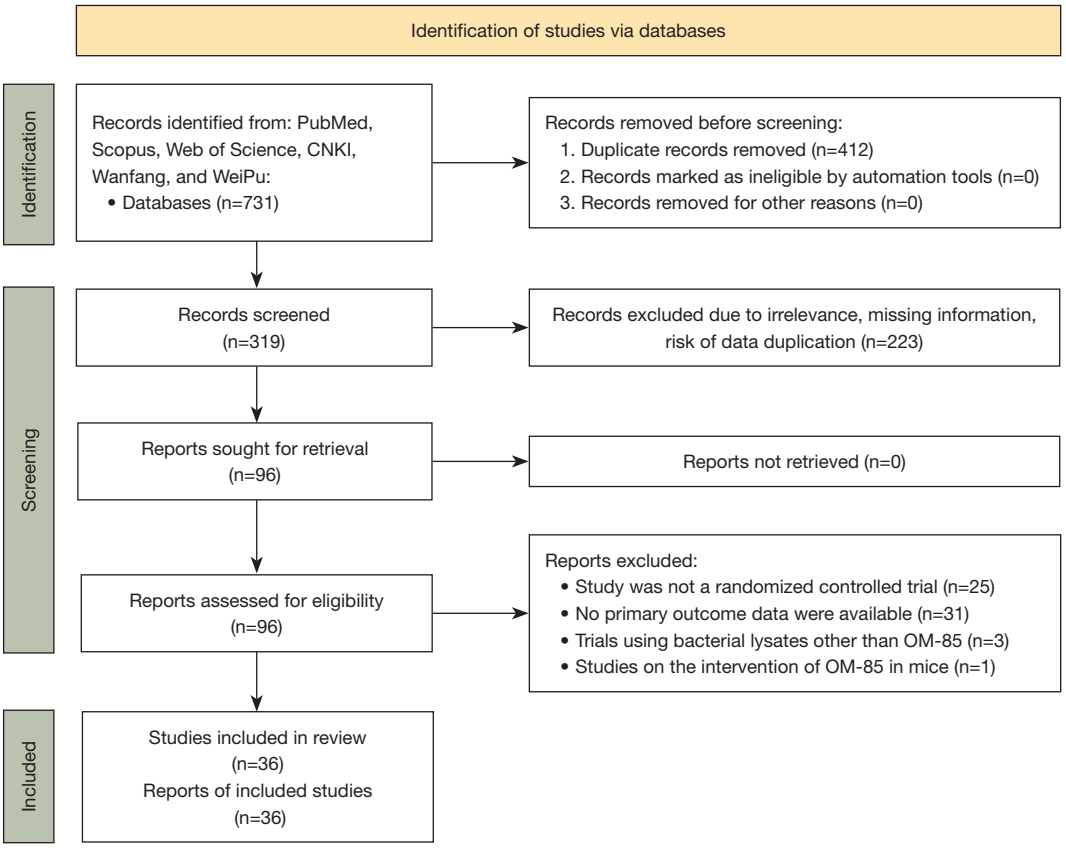

Figure 1 Literature search and selection process.

participants was insufficient for assessing the risk of bias. In addition, unblinding of trial interventions may have also led to bias in non-quantitative data such as clinical symptoms (*Figure 2A*,*2B*).

Clinical symptoms of asthma

A total of 19 randomized controlled trials (RCTs) were included in our analysis in order to determine the efficacy of treatment using oral administration of OM-85; we then assessed the number of asthma clinical symptoms, including wheezing and coughing, before and during treatment. There were 898 patients (of whom 817 were children) in the OM-85 treatment group and 879 patients (of whom 798 were children) in the control group. As shown in *Figure 3*, improvement in total asthma clinical symptoms was 24% greater in the OM-85 treatment group than in the control group (RR =1.23, 95% CI: 1.18–1.28). A subgroup of adult patients showed a 36% improvement in asthma clinical symptoms (RR =1.36, 95% CI: 1.16–1.59), which was higher than the 22% improvement in asthma clinical symptoms observed in a subgroup of pediatric patients (RR =1.22, 95% CI: 1.17–1.27). However, thus far, only two randomized controlled trials have been performed to assess the use of OM-85 in adult patients with asthma; therefore, more clinical trial data are needed to confirm that OM-85 shows greater effectiveness in ameliorating the clinical symptoms of asthma in adult patients than in pediatric patients (*Figure 3A*).

As shown in *Figure 3B*, the total number of asthma exacerbations in the experimental group was significantly reduced after treatment using OM-85 compared with that in the control group (SMD: –1.43, 95% CI: –1.62 to –1.24). Subgroup analysis showed that children presented significant reductions in asthma exacerbations after treatment using OM-85 (SMD: –1.78, 95% CI: –1.99 to –1.57). In contrast, a subgroup of adults, included in only one RCT, paradoxically showed a slightly increased number of asthma exacerbations after treatment using OM-85 (SMD: 0.2, 95% CI: 0.25–0.65).

Table 1 Characteristics of included studies

Study	Publisher year	Treatment group (N)	Control group (N)	Treatment group intervention	Control group intervention	Treatment duration (days)	Age (year)		End points
							Treatment group	Control group	
Feng Suzhi (10)	2020	45	45	OM-85 + budesonide aerosol	Budesonide aerosol	90	26.24±3.47	26.28±3.51	1,4,9
Song Jiafu (11)	2010	15	15	OM-85 + salmeterol fluticasone propionate inhalation	Salmeterol fluticasone propionate inhalation	30	35.6 (mean)	37.1 (mean)	3,6
Yuan Junhui (12)	2007	15	15	OM-85 + routine therapies	Routine therapies	90	4±1.2	7.1±1.5	4,5,9
Cao Jian (13)	2016	36	36	OM-85 + terbutaline sulfate aerosol combined with budesonide aerosol	Terbutaline sulfate aerosol combined with budesonide aerosol	10	35.4±8.2	39.9±10.4	1,5,8
Zhang Tian (14)	2018	48	47	OM-85 + routine therapies	Routine therapies	90	6.2±0.5	5.8±0.7	1,8
Lv Yanqing (15)	2016	58	58	OM-85 + routine therapies	Routine therapies	21	6.4±1.2	6.8±1	1,3,4,8
Wu Xiaoxu (16)	2020	60	60	OM-85 + beclomethasone propionate aerosol	Beclomethasone propionate aerosol	90	5.9±2.2	6.3±2.5	1,3,8,9
Zhang Zhiying (17)	2021	50	40	OM-85 + routine therapies	Routine therapies	30	5.53±1.06	4.17±1.32	3,8
Chen Yang (18)	2015	67	54	OM-85 + routine therapies	Routine therapies	21	5.2±2.2	5.4±2.1	1,4,7,8,9
Li Xia (19)	2017	52	52	OM-85 + budesonide aerosol	Budesonide aerosol	90	7.35±2.11	7.92±2.39	1,4,9
Mao Chengli (20)	2020	42	41	OM-85 + routine therapies	Routine therapies	14	8.84±5.23	8.81±5.26	1,4,8
Yang Fen (21)	2017	43	43	OM-85 + routine therapies	Routine therapies	21	5.3±2.06	5.02±1.82	1,4
Zhang Huiyu (22)	2007	36	37	OM-85 + routine therapies	Routine therapies	90	1.3±0.31	1.3±0.31	2,5,9
Hu Peiling (23)	2011	47	46	OM-85 + fluticasone propionate aerosol	Fluticasone propionate aerosol	90	7.78±2.29	8.04±1.84	2,5,8,9
Chen Zhuanggui (24)	2009	29	16	OM-85 + inhaled corticosteroids	Inhaled corticosteroids	90	5–12	6–14	2,3,5,8
Li Xianqing (25)	2017	32	32	OM-85 + leukotriene modifiers + inhaled corticosteroids	inhaled corticosteroids	90	8.2±1	7.9±0.8	1,4,7
Zhang Shuilin (26)	2014	31	33	OM-85 + montelukast	Montelukast	90	6.6±2.1	6.7±2.7	3,5,8
Gao Yuan (27)	2010	87	86	OM-85 + montelukast	Montelukast	90	3.67 (mean)	3.67 (mean)	2,4,5,6,9
Hao Lixia (28)	2016	41	42	OM-85 + leukotriene modifiers + inhaled corticosteroids	inhaled corticosteroids	56	8.4±1.3	8.7±1.1	1,4,7,9
Song Jiafu (29)	2011	15	12	OM-85 + salmeterol fluticasone propionate aerosol	Salmeterol fluticasone Propionate aerosol	90	35±10	38±7	3,6

Table 1 (*continued*)

Table 1 (*continued*)

Study	Publisher year	Treatment group (N)	Control group (N)	Treatment group intervention	Control group intervention	Treatment duration (days)	Age* (year)		End points
							Treatment group	Control group	
Xiong Mingmei (30)	2013	30	30	OM-85 + salmeterol fluticasone propionate aerosol	Salmeterol fluticasone Propionate aerosol	60	29.42±9.58	28.18±10.31	3,6
Zhang Wei (31)	2015	17	16	OM-85 + inhaled corticosteroids	Inhaled corticosteroids	30	1–12	1–12	2,3
Li Yi (32)	2020	66	66	OM-85 + routine therapies	Routine therapies	30	22±0.7	22±0.5	1,9
Yang Xin (33)	2017	44	44	OM-85 + budesonide aerosol	Budesonide aerosol	21	6.28±1.31	6.35±1.17	1,3,4,8,9
Qian Donglin (34)	2020	52	53	OM-85 + budesonide aerosol	Budesonide aerosol	21	5.77±1.47	5.92±1.55	1,7,8
Liao Jiayi (35)	2014	31	31	OM-85 + inhaled corticosteroids	Inhaled corticosteroids	360	4.5±0.7	4.5±0.6	5,9
Cai Jierong (36)	2020	37	37	OM-85 + budesonide aerosol	Budesonide aerosol	90	2.13±0.46	2.21±0.57	1,5
Yang Liwei (37)	2020	68	68	OM-85 + routine therapies	Routine therapies	90	6.16±2.57	6.59±2.37	3,4,7,9
Wang Pingsheng (38)	2021	45	40	OM-85 + salbutamol aerosol	Salbutamol aerosol	90	7.06±2.01	7.59±1.89	1,3,4,9
Tang Yuqi (39)	2017	44	43	OM-85 + inhaled corticosteroids	Inhaled corticosteroids	120	7.8±2	7.6±1.9	1,3,8
Yang sibo (40)	2020	42	42	OM-85 + routine therapies	Routine therapies	90	10.18±0.96	10.52±1.03	1,3,4,8
Zhang Yujing (41)	2011	46	20	OM-85 + routine therapies	Routine therapies	90	2.5 (mean)	2.5 (mean)	2,5,9
Zhang Hua (42)	2019	44	44	OM-85 + inhaled corticosteroids	Inhaled corticosteroids	30	6.73±0.82	6.45±0.74	1,3
R.-F. Han (43)	2016	74	62	OM-85 + routine therapies	Routine therapies	90	2.3±0.6	2.2±0.4	2,8
Geertje M. de Boer (44)	2021	38	37	OM-85	Placebo	180	40.00 (28.0–51.3)	41.0 (31.5–54.5)	3,5,7,8
Lu Yanming (45)	2014	24	36	OM-85 + inhaled corticosteroids	Inhaled corticosteroids	270	8.9±2.8	8.7±2.7	2,5,7,8,9

*, Data are shown as mean ± SD, range, or median (interquartile range). Endpoints: 1, improvement of asthma symptoms; 2, the number of asthma attacks; 3, lung function; 4, level of T-lymphocyte subsets; 5, the level of serum immunoglobulin; 6, the level of sputum siga; 7, the level of serum EOS or ECP; 8, the level of cytokines; 9, adverse event. Age is shown as mean ± SD or mean. EOS, eosinophil; ECP, eosinophil cationic protein; SD, standard deviation.

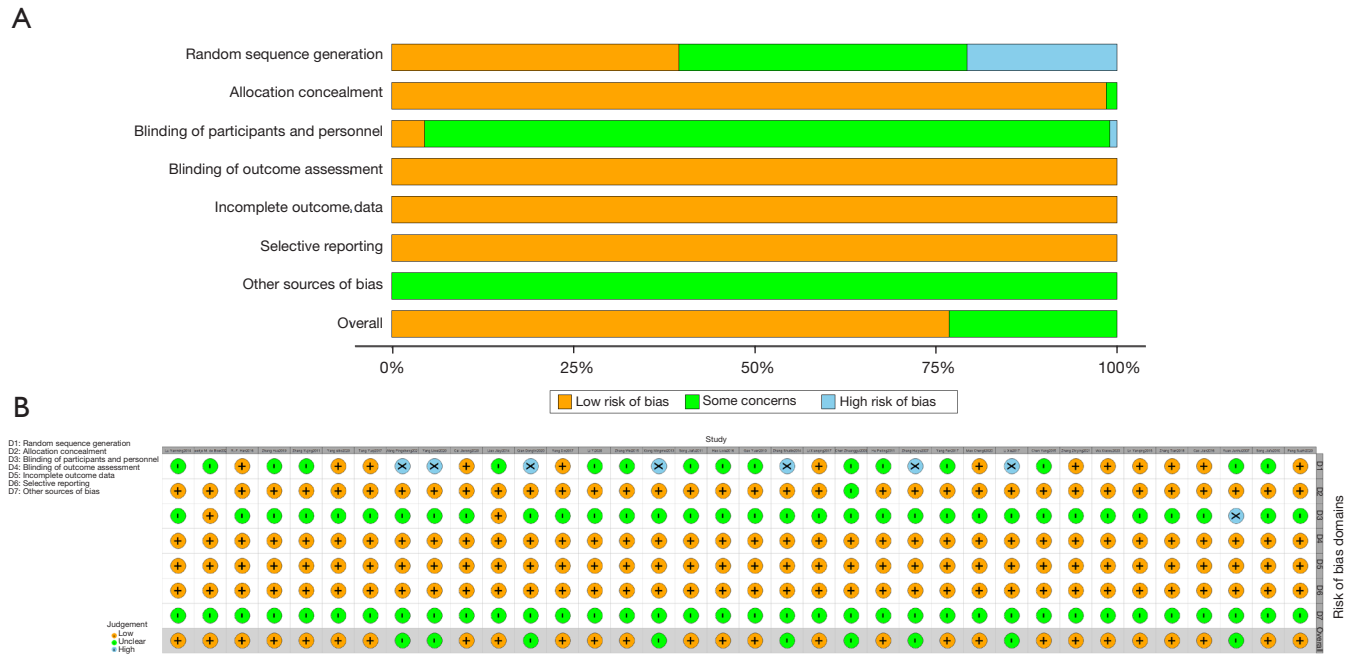

Figure 2 Risk of bias was assessed using the Cochrane risk of bias assessment tool. (A) The summary of risk of bias; (B) each risk of bias item for each included study.

Lung function

Treatment using OM-85 improved percent predicted FEV_1 (FEV_1%) (SMD: 0.65, 95% CI: 0.47–0.84), FEV_1 (SMD: 0.63, 95% CI: 0.48–0.77), FEV1/forced vital capacity (FVC) (SMD: 0.27, 95% CI: −0.10 to 0.63), FVC (SMD: 0.44, 95% CI: 0.19–0.69), and Peak expiratory flow (PEF) (SMD: 0.62, 95% CI: 0.48–0.76) in patients with asthma. Interestingly, a subgroup of children showed greater improvement in FEV_1% (SMD: 0.90, 95% CI: −0.68 to 1.13), compared with the improvement in FEV_1% of adult subjects (SMD: 0.10, 95% CI: −0.24 to 0.43) (Figure S1).

Levels of T-lymphocyte subsets

The children treated with OM-85 showed increased levels of $CD3^+$ (SMD: 1.59, 95% CI: 1.45–1.73), $CD4^+$ (SMD: 1.63, 95% CI: 1.49–1.76), and $CD4^+/CD8^+$ (SMD: 1.12, 95% CI: 1.00–1.24), as well as decreased concentrations of $CD8^+$ (SMD: −2.38, 95% CI: −2.58 to −2.17) compared with those without OM-85 add-on therapy (Figure S2).

Levels of serum immunoglobulin and sputum sIgA

Patients with OM-85 add-on therapy presented higher serum levels of IgA (SMD: 1.11, 95% CI: −0.58 to 1.64), IgG (SMD: 0.34, 95% CI: 0.19–0.49), IgM (SMD: 0.26, 95% CI: 0.11–0.42), and total sputum sIgA (SMD: 0.2, 95% CI: 0.25–0.65), and slightly decreased levels of IgE (SMD: −0.12, 95% CI: −0.49 to −0.24) compared to the controls. Moreover, subgroup analysis showed significantly higher levels of sputum sIgA (SMD: 3.56, 95% CI: 3.18–3.93) in children than in adults (SMD: 1.05, 95% CI: 0.58–1.51). But there were significantly lower levels of serum IgM in children (SMD: 0.18, 95% CI: 0.00–0.36) than in adults (SMD: 0.54, 95% CI: 0.21–0.87) (Figure S3).

The number of peripheral EOS and the levels of ECP and serum cytokine

Regarding eosinophilic inflammation, OM-85 add-on therapy decreased the total number of peripheral EOS (SMD: −1.33, 95% CI: −1.56 to −1.10) and the levels of ECP (SMD: −2.06, 95% CI: −2.33 to −1.78). Intriguingly, children showed a stronger intensity of reduction in peripheral EOS number (SMD: −1.85, 95% CI: −2.11 to −1.59) compared than adults (SMD: 0.22, 95% CI: −0.23 to 0.67). Additionally, our data showed that OM-85 add-on therapy decreased the levels of interleukin-4 (IL-4) (SMD:

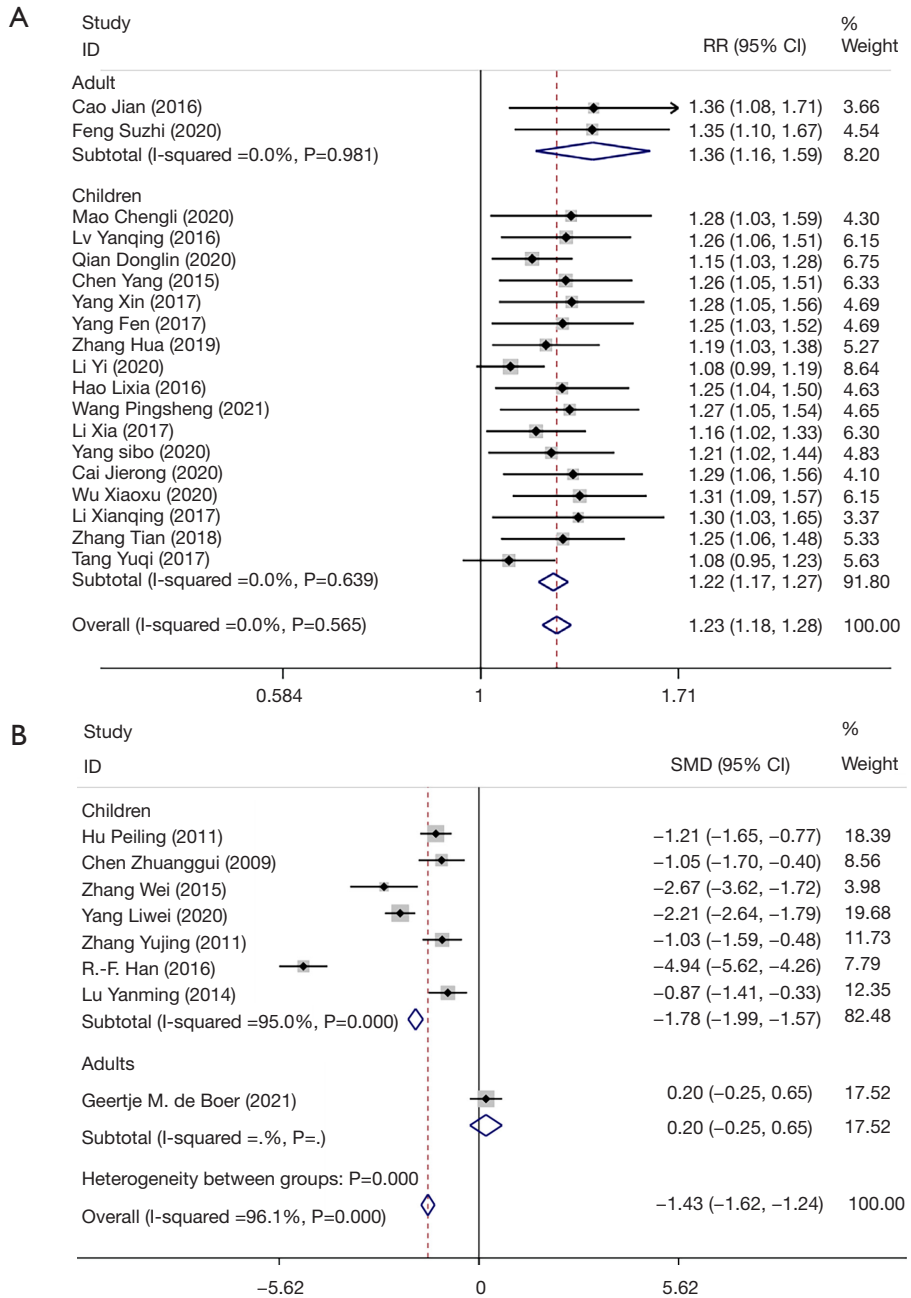

Figure 3 Forest map of clinical symptoms of asthma. (A) The proportion of improvement in asthma clinical symptoms; (B) the number of asthma exacerbations during treatment.

−1.79, 95% CI: −1.94 to −1.64) and IL-5 (SMD: −2.75, 95% CI: −5.08 to 0.41), whereas increased the concentrations of IL-10 (SMD: 1.29, 95% CI: 0. 91–1.67), IL-12 (SMD: 2.46, 95% CI: 1.79–3.12), and IFN-γ (SMD: 1.34, 95% CI: 1.19–1.48). Similarly, children either presented a greater decrease in IL-4 levels (SMD: −1.92, 95% CI: −2.08 to −1.76) or a higher increase in IFN-γ levels (SMD: 1.40, 95% CI: 1.25–1.56) than adults (Figure S4).

Adverse events

Fifteen trials compared the incidence of adverse events

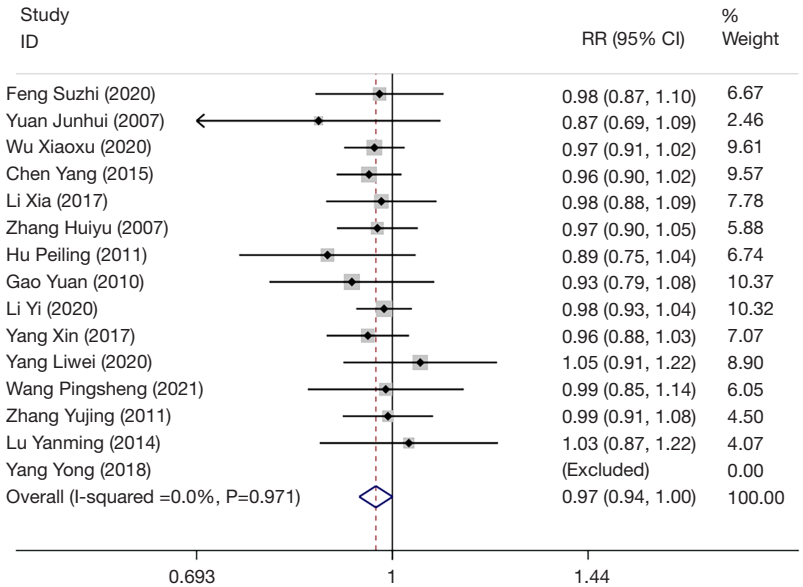

Figure 4 Adverse event.

in the experimental and control groups by recording the number of times the patients experienced symptoms such as dizziness, somnolence, nausea, diarrhea, and rash during the 85-OM add-on therapy period. The results showed no significant differences in the incidence of adverse events between patients treated with OM-85 and the control group (RR: 0. 97, 95% CI: 0.94–1.00) (*Figure 4*).

Publication bias

Figure S5 shows the generated funnel plots. In the add-on therapy in the OM-85 and control groups, publication bias was readily discernable in the number of asthma exacerbations during treatment, as well as in the FEV1, $CD3^+$, $CD8^+$, and sputum sIgA levels. Despite the increase in OM-85 studies over the last 2 years, the mechanism underlying OM-85 add-on immunoregulatory therapy remains unclear. There is still a small study effect and more high-quality clinical studies are needed.

Sensitivity analysis

Sensitivity analysis showed that most of the parameters of sensitivity analysis have good stability and robustness. However, several sets of results indicated high sensitivity and heterogeneity. Detailed parameters for each sensitivity analysis are shown in Figure S6.

Heterogeneity

The degree of improvement in the clinical symptoms of asthma, FEV_1, FVC, PEF, serum IgE levels, and adverse events associated with treatment using OM-85 showed little heterogeneity, but all other included variables did (I^2>50%). This heterogeneity might have come from any of several factors, such as the demographic and clinical characteristics of included patients, differences in basic treatment, time of symptom onset, laboratory parameters measured, and treatment interventions before admission. Due to the insufficient number of studies on OM-85, we did not further analyze the sources of high heterogeneity in the individual results.

Discussion

Our updated meta-analysis demonstrated that OM-85 add-on therapy could significantly improve asthmatic symptoms, decrease the number of asthma exacerbations, and reduce airway dysfunction. Additionally, treatment with OM-85 showed immune-modulatory effects indicated by elevated levels of serum immunoglobulins, increased numbers of T-lymphocytes and their subsets, and decreased levels of IL-4. Notably, for the first time, we observed that the effects of OM-85 were more prominent in asthmatic children than in adults based on the findings of subgroup analysis. Collectively, OM-85 add-on therapy shows promise as an asthma treatment. Our results indicate that OM-85 has potential applications

in anti-asthma therapy, especially in asthmatic children with recurrent airway infections and poor disease control.

OM-85 is composed of non-viable bacterial extracts obtained by chemical lysis of bacterial cultures and lyophilization (46). Orally administered OM-85, absorbed through the gastrointestinal tract, is an effective stimulant that activates the innate and adaptive arms of the immune system, and leads to functional immune responses against the invading pathogens. Since the 1950s, OM-85 has been widely used for the prevention of recurrent respiratory tract infections in several European and Asian countries (47-49). Respiratory tract infection is a major predisposing factor that contributes to asthma exacerbations. Statistically, up to 50% of asthma exacerbations are elicited by respiratory tract infections (50). Because of the imbalanced T1/T2 inflammatory responses observed in asthma, patients with asthma are predisposed toward respiratory tract infections, which causes symptom worsening, decline of pulmonary function, and poor disease control (51). Therefore, strengthening and repair of the airway immune function may be a crucial strategy in asthma treatment. Our results show that add-on treatment using OM-85 was effective in relieving the symptoms of asthma, reducing the number of asthma exacerbations, and improving airway function. Due to immune-modulatory effects of OM-85, detailed application of OM-85 in asthma treatment warrants further study, especially in pediatric patients with recurrent airway viral infections and in adult patients with comorbidities such as chronic obstructive pulmonary disease, chronic bronchitis, and bronchiectasis.

Thus far, the working mechanisms of OM-85 have not been fully characterized. Based on evidence obtained *in vitro*, in animal models, and in studies of numerous human diseases, the following four cellular mechanisms may be responsible for the clinical effects of OM-85: gut-associated lymphoid tissue (GALT)-mediated activation of dendritic cells, T-lymphocytes, and B-lymphocytes; GALT-generated migration of immune cells into the upper and lower respiratory tract; increased production of immunoglobulins resulting in decreased susceptibility to pathogens; and correction of an imbalance in T1/T2-mediated inflammation (7,52-54). Based on our data, the OM-85 add-on therapy did present immunomodulatory effects such as increased numbers of T-lymphocytes, increased IgA concentration in serum and sputum, elevated levels of T1 inflammatory cytokines, and decreased intensity of T2-mediated inflammatory responses. Although the current study could not discover the potential mechanism, the changes in above immune parameters might serve as an indicator of treatment efficacy and predictor of disease aggression. More basic research is warranted to explore the working mechanisms.

Another finding showed that OM-85 add-on therapy presented more prominent effects in children, compared with those in adults, with asthma. From the time the newborn passes through the birth canal of the mother, humans are continuously exposed to probiotic or harmful bacteria in the external environment via various routes such as the mouth, skin, and respiratory tract. Various bacteria colonizing mucosal sites are essential for healthy human growth; these bacteria also affect the development of the immune system. Intestinal bacteria influence the development of Th17 (55,56), Treg (57), and memory T cells (58-61). Approximately 20% of lymphocytes residing in the gut are exposed to numerous possible foreign immunogens, which affects the occurrence and development of allergic diseases (62-64). Therefore, dysfunction immune homeostasis is considered a major cause of disease development. OM-85 contains numerous pathogen-associated pattern molecules that participate in restoring equilibrium to an impaired immune homeostasis. Given the unformed immune homeostasis in children, the treatment using OM-85 in children seemed to be more advantageous then using it in adults. Additionally, oral OM-85 is well tolerated and shows a good safety profile. Hence, OM-85 can be administered empirically to control or reduce wheezing in children who have not been diagnosed with asthma, especially children who are too young to cooperate with clinical tests, such as tests of lung function. Concurrently, OM-85 can also be used as an adjunct therapy in addition to routine therapy in adult asthma patients.

OM-85 is a mixed lysate of several fixed bacterial genera; it is currently one of the few such therapeutics prepared using standard processes. With improved understanding of immune development, we may be able to optimize the route and timing of bacterial lysate administration, and determine the immunologic mechanisms mediated by these treatment modalities in order to optimize intervention.

Other recent studies support our current findings (65,66). Our present study contributes to existing clinical data on patients with asthma, and to the best of our knowledge, is the first such study to include an adult subgroup treated with OM-85 in a meta-analysis. However, our present study had several limitations. In our meta-analysis, we included a large number of studies conducted in China. Furthermore, unclear descriptions of methodology and study design, and high risk of bias, were present in some of the studies

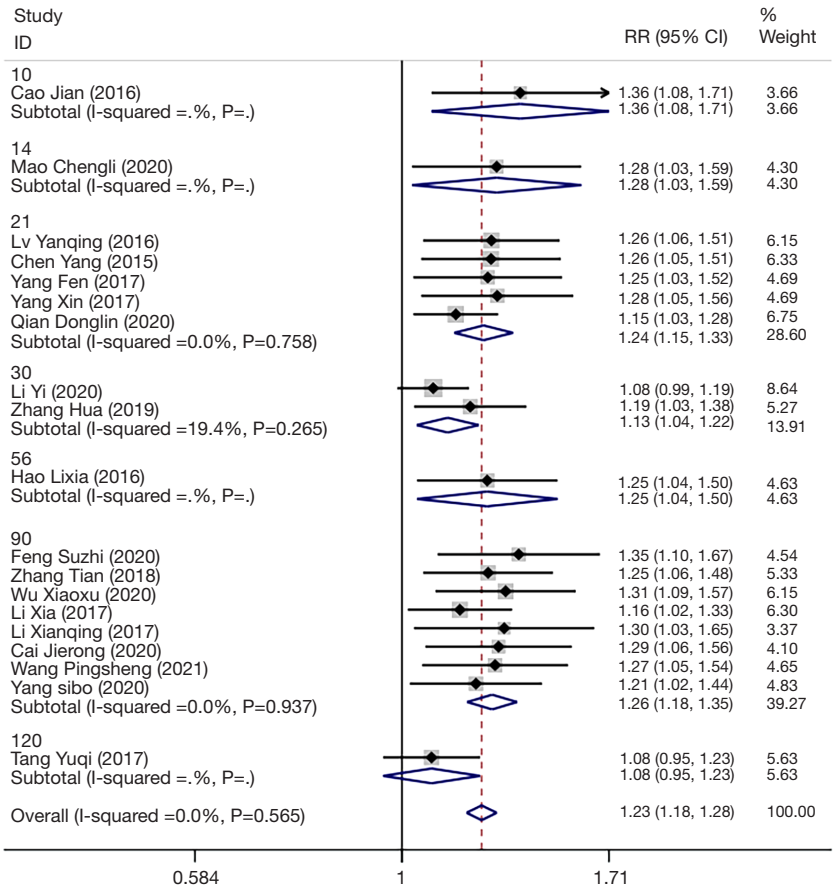

Figure 5 Proportion of improvement in clinical symptoms of asthma (subgroup analysis of treatment duration).

included in our analysis. Thus, the strength of the obtained results may be low for some of the data. In the studies we included, the duration of OM-85 treatment varied widely. For example, the longest treatment period was 360 days and the shortest was only 10 days. We analyzed the improvement in asthma clinical symptoms relative to duration of treatment as subgroups. As shown in *Figure 5*, there were no significant differences in the improvement of the clinical symptoms of asthma as OM-85 treatment continued. However, we still need more study and data for each subgroup to increase the solidity of this conclusion. In addition, a considerable proportion of analyzed results had moderate or high heterogeneity. Finally, there were only five studies investigating the clinical efficacy of OM-85 in adult patients with asthma. Further analysis of existing literature is required to show whether OM-85 exerts differential therapeutic effects in adults and children with asthma. In summary, our study included numerous studies as sources of analytical data. The various laboratory and lung function tests examined in our current study helped demonstrate the effectiveness of OM-85 as an add-on treatment in asthma. Our analysis of the number of asthma exacerbations, lung function, T lymphocyte subsets, serum immunoglobulin levels, serum EOS numbers, serum IL-4 levels, and other indicators showed that OM-85 was more efficacious in the treatment or control of wheezing in children than as an add-on treatment in adult asthma.

Conclusions

The results of analysis performed in our present study suggest that OM-85 add-on therapy shows promising immunomodulatory effects that significantly improve asthma symptoms and lung function. The clinical benefits of OM-85 add-on treatment seemed to be more pronounced for asthmatic children than adults with asthma. Further studies focusing on the immunomodulatory function of OM-85 in asthma personalized treatment are warranted.

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Footnote

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