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Research on Depression in Children with Severe Bronchial Asthma: The Impact of Alexithymia and Somatic Symptoms

ABSTRACT

Objective: The prevalence of depression in children with severe bronchial asthma is a significant concern due to its potential effects on illness burden and quality of life. This cross-sectional study aims to explore the relationship between depression and severe bronchial asthma in children, focusing on the impact of alexithymia and somatic symptoms.

Methods: The study includes a total of 186 children aged 6-14 years diagnosed with severe bronchial asthma between 2008 and 2022 in our institute. Alexithymia was assessed using the Toronto Alexithymia Scale—20 items (TAS-20). Somatization symptoms were measured using the children's somatization inventory (CSI). The Hamilton depression scale (HAMD) was used to evaluate depression. Spearman correlation analysis was used to describe the correlation between alexithymia, somatization symptoms, and depression.

Results: Children with bronchial asthma are found to have a significantly higher prevalence of depression, estimated to be around 16.67%. Approximately 98.92% of children exhibit varying degrees of somatic symptoms. Approximately 3.23% of children have alexithymia. The Spearman correlation analysis revealed that somatic symptoms and alexithymia were positive correlated with the depression. The correlation coefficients were 0.986 and 0.981 ($P < .01$), respectively. moreover, according to the results of multiple linear regression analysis, somatization symptoms and alexithymia significantly affects depression in children with severe bronchitis asthma ($P < .01$).

Conclusion: These findings suggest that children with severe bronchial asthma experience a higher prevalence of depression, impacting their overall quality of life. In addition, the presence of somatic symptoms is prevalent among these children, further contributing to the burden on their quality of life. Moreover, somatization symptoms and alexithymia have been identified as a significant factor positive affecting depression in this population. Addressing these factors in clinical interventions may be beneficial for improving the overall well-being in this population.

Keywords: Bronchial asthma, depressive syndrome, somatic symptoms, alexithymia

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Introduction

Severe bronchial asthma is prevalent respiratory disorders in children, often leading to significant morbidity and depression.[1] These conditions can have profound physical and psychological effects on affected individuals, especially children, impacting their overall well-being and daily functioning.[2,3] While much research has focused on the physical symptoms associated with these conditions, such as coughing, wheezing, and shortness of breath, there is a lack of understanding regarding the influence of somatic symptoms and alexithymia on the depression outcomes in children with severe bronchial asthma.[4]

Depression is a significant mental health concern among children with severe bronchial asthma, contributing to diminished quality of life and increased burden on healthcare resources. Understanding the factors that influence depression in this population is crucial for

developing targeted interventions and improving patient outcomes. Although the relationship between asthma and depression has been recognized, limited research has explored the specific impact of alexithymia and somatic symptoms on depression in these children.

Somatic symptoms refer to physical complaints without a clear organic basis, including headaches, stomachaches, and muscle pain. These symptoms can be distressing for children and may lead to limitations in daily activities and school functioning. Alexithymia is a construct that refers to difficulties in recognizing and expressing emotions. Children with alexithymia may struggle to understand and describe their own emotional experiences, which can impact their ability to cope with stressors and navigate social interactions effectively.[5] As a result, studies have shown that children with chronic illnesses, including respiratory diseases, have higher risk levels of somatic symptoms compared to their healthy peers, especially children aged 6-14 who face social influences on their mental state.[6,7] Although alexithymia has been explored in various clinical populations, its potential effect on depression in children with severe bronchial asthma remains relatively understudied.

This study aims to investigate the prevalence of depression and examine the associations between alexithymia, somatic symptoms, and depression in children with severe bronchial asthma. The findings will provide valuable insights into the complex interplay between mental and physical health in this population, informing the development of comprehensive care strategies to address the unique challenges they face. By understanding the impact of somatic symptoms and alexithymia on depression of children with severe bronchial asthma, healthcare professionals can better tailor interventions and management strategies to improve their overall well-being.

Material and Methods

Participants

Children with severe bronchial asthma attending our hospital from May 2008 to January 2022 were included in this study. Inclusion criteria: (a) the diagnosis of bronchial asthma in children was based on the 2016 edition of the Guidelines for the Diagnosis and Prevention of Bronchial Asthma in Children;[8] (b) a review of clinical signs and the results of pulmonary function tests was conducted; (c) the patients were capable of reading and writing comprehension, as well as answering the survey completely; and (d) age 6-14 when social influence appears.[8] Exclusion criteria: (a) the patient was diagnosed with mental abnormality, cognitive impairment, and autonomic dysfunction by doctors at or above the attending level; (b) the patient had a serious infection; the patient had other significant respiratory diseases such as lung cancer, Chronic obstructive pulmonary disease (COPD), and cystic fibrosis. All children's parents signed a written informed consent form; and (c) incomplete clinical and follow-up information.

MAIN POINTS

- *Children with severe bronchial asthma experience a higher prevalence of depression, impacting their overall quality of life.*
- *Presence of somatic symptoms is prevalent among these children, further contributing to the burden on their quality of life.*
- *Somatization symptoms and alexithymia has been identified as a significant factor positive affecting depression in this population.*

Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Hangzhou Red Cross Hospital (Approval Number: 2023115, Date October 8, 2023). All children's parents signed a written informed consent form.

Tools

The children's depression was assessed using the Hamilton Depression Scale (HAMD), and this questionnaire has good reliability and validity.[9] The HAMD is a widely used tool in clinical research and practice to assess the severity of depressive symptoms. It consists of 17 items that evaluate various aspects of depression, including mood, guilt, suicide, sleep disturbances, anxiety, weight loss, and cognitive impairment. Each item is rated on a scale of 0 to 4 or 0 to 2, depending on the specific item. The total score on the HAMD can range from 0 to 52, with higher scores indicating more severe depressive symptoms. Severity levels of HAMD scores are as follows: total score ≤7 points: no depression; total score 8-17 points: possible depression; total score 18-24 points: definite depression; total score ≥25 points: severe depression.

Somatization symptoms were assessed using the Children's Somatization Inventory (CSI) which has good reliability and validity for children.[10] The CSI consists of 42 items divided into 4 factors: gastrointestinal symptoms, pain/weakness symptoms, cardiovascular and other symptoms, and pseudo-neurological symptoms. Each item is scored on a 3-point scale ("0" indicating "never or rarely," "1" indicating "sometimes or mild," and "2" indicating "often or severe"). The sum of scores for all items represents the total score of somatization symptoms, ranging from 0 to 84. A higher score indicates a higher level of somatization within the past 3 months. The CSI has been found to have a Cronbach's alpha coefficient of 0.87, indicating high internal consistency.[11] Additionally, it has a correlation coefficient of 0.73 with the Parents Version of the CSI (PCSI), which is a somatization inventory completed by parents.

The 20-item Toronto Alexithymia Scale (TAS-20) is a questionnaire used to assess alexithymia, which refers to difficulties in identifying and describing emotions, as well as externally oriented thinking (EOT).[12] It evaluates emotional disorders based on the following 3 aspects: (a) Difficulty in Emotion Identification (DIE): consisting of 7 items; (b) Difficulty in Emotion Description (DDE): consisting of 5 items; and (c) EOT: consisting of 8 rating items. Each item is rated on a 1 to 5 scale. The scores gradually increase to represent increasing degrees from "strongly disagree" to "strongly agree." The lowest score on this scale is 20, and the highest score is 100. A higher score indicates a more severe level of emotional disorder.

The Chinese version of TAS-20 has good reliability and validity indicators.[13] Its Cronbach's alpha coefficient is 0.83. The test-retest reliability is 0.87, suggesting good stability over time. The correlation coefficients between each factor and the total score range from 0.72 to 0.82, indicating a strong association.

Statistical Analysis

The statistical data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Corp., Armonk, NY, USA). We calculated the minimum sample size through the formula $n = (Z\alpha + Z\beta)^2 \times 2/$ (Cohen's d)^2, and this study met the

requirement of the minimum sample size n = 68. Descriptive statistics, such as mean ± SD, were used to represent continuous variables. Shapiro–Wilk test was used to test the normal distribution of continuous variables, Pearson analysis was used for normal distribution, and Spearman correlation analysis was used to test the relationship between variables for non-normal distribution. Multiple linear regression analysis was utilized for multivariate analysis. A significance level of $P < .05$ was considered statistically significant for all analyses.

Results

Socio-demographic Characteristics of the Children's Patients

This cross-sectional study included a total of 186 children with severe bronchial asthma. Among them, there were 98 male children (52.69%) and 88 female children (47.31%). The age range was between 6 and 14 years, with an average age of (8.8 ± 1.9) years. The body weight was (34.18 ± 7.02) kg. The clinical diagnosis was severe bronchial asthma, with an average duration of 3.47 ± 0.58 years (Table 1).

The Prevalence of Depression Among Children with Bronchial Asthma

In terms of the prevalence of depression within a specific population, the table presents data indicating that out of the total number of individuals evaluated, 155 individuals (83.33%) displayed no indications of depression. Furthermore, 20 individuals (10.75%) were categorized as having possible depression, indicating the presence of certain depressive symptoms. In addition, 7 individuals (3.76%) received a diagnosis of definite depression, which signifies a more pronounced manifestation of depressive symptoms. Lastly, 4 individuals (2.15%) exhibited severe depression, representing the highest level of severity among the assessed individuals. These findings indicate elevated risk of depression among children with bronchial asthma. The coexistence of these conditions can further complicate the management of asthma symptoms, potentially leading to worsened physical and psychological well-being.

Alexithymia in Children with Severe Bronchial Asthma

To further investigate the extent of emotional disorder in children with severe bronchitis, this study divided the patients into 3 groups based on their TAS-20 scores: (a) alexithymia group (≥61 points, n = 3); (b) possible alexithymia group (52-60 points, n = 3); and (c) non-alexithymia group (≤51 points, n = 180). The distribution of TAS-20 scores in patients with severe bronchial asthma is shown in Figure 1.

Table 1. Descriptive Statistics for Demographic Characteristics of Children with Severe Bronchial Asthma

Variables	n or Mean(±SD)
Age (years)	10.5 (± 2.5)
Body weight (kg)	34.18 (± 7.02)
BMI (kg/m^2)	20.49 (± 2.26)
<24	164 (88.17%)
≥24	22 (11.83%)
Gender	
Male	98 (52.69%)
Female	88 (47.31%)
Smoke	
Male	5 (2.69%)
Female	2 (1.08%)
History of mental illness	13 (6.99%)

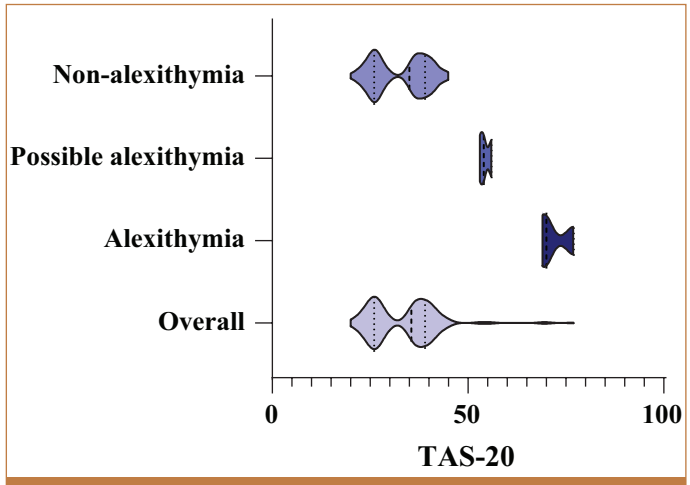

Figure 1. Violin plot of TAS-20 scores in different groups. The length of the graph represents the dispersion of TAS-20 scores within each group, while the width represents the probability of a specific score.

Overall Distribution of Severity Levels of Somatization in Children

Among the 186 research participants, only 2 individuals (1.08%) did not experience any somatization symptoms. Most participants, 184 (98.92%), exhibited varying degrees of somatization symptoms, with one or more symptoms present. Interestingly, it is evident that the severity level of somatization in children follows a positively skewed distribution. The highest somatization score recorded was 48, while the lowest score observed was 0. On average, the participants had a somatization score of (21.09 ± 5.23).

Analysis of the Relationship Between Somatic Symptoms and Depression in Children with Severe Bronchial Asthma

According to Table 2, it is evident that there is a significant correlation between the total scores of depression in children and the total score of somatic symptoms, ($r = -0.986$, $P < .01$). This negative correlation suggests that higher levels of somatic symptoms are associated with more severe depression in children with severe bronchial asthma.

Furthermore, it can be observed that most of the sub-dimensions of depression are positively correlated with different dimensions of somatic symptoms ($P < .05$). However, it should be noted that most correlation coefficients remain below 0.4, indicating a moderate association between these variables.

These findings highlight the importance of considering both somatic symptoms and depression in children with severe bronchial asthma. The presence of somatic symptoms can have a detrimental impact on various aspects of a child's quality of life, such as their physical functioning, emotional well-being, and social interactions.

Analysis of the Relationship between Alexithymia and Depression in Children with Severe Bronchial Asthma

Based on the findings presented in Table 3, a noteworthy observation is the significant correlation ($r = 0.981$, $P < .01$) between the total scores of depression in children and the total score of alexithymia. This positive correlation strongly indicates that higher levels of alexithymia are closely linked to depression in children.

Table 2. Correlations between Somatic Symptoms and Depression in Children

	Pain/Weakness Symptoms	Cardiovascular and Other Symptoms	Functional Neurological Symptoms	Gastrointestinal Symptoms	Total
Depressive mood	0.342**	0.231*	0.380**	0.174*	0.365**
Feelings of guilt	0.437**	0.298**	0.355**	0.271**	0.421**
Suicidal thoughts	0.159	0.212*	0.084	0.079	0.201**
Difficulty falling asleep	0.193	0.209*	0.285**	0.264**	0.339**
Shallow sleep	-0.082	0.184	0.159	0.140	0.137
Early awakening	0.244*	0.185	0.233*	0.223**	0.308**
Impairment in work and interests	0.295**	0.292**	0.256*	0.125	0.314**
Sluggishness	0.293**	0.076	0.189	0.218**	0.303**
Restlessness	0.404**	0.212*	0.223*	0.116	0.251**
Mental anxiety	0.337**	0.030	0.113	0.229	0.214**
Somatic anxiety	0.354**	0.227*	0.240**	0.195**	0.380**
Gastrointestinal symptoms	0.270**	0.267**	0.257*	0.125	0.339**
General physical symptoms	0.279**	0.159	0.149*	0.111	0.244**
Sexual symptoms	0.049	0.218*	0.324**	0.220**	0.329**
Hypochondria	0.156	0.228*	0.224**	0.252**	0.251**
Weight loss	0.361**	0.320**	0.224**	0.158*	0.373**
Insight into one's own condition	0.169	0.193	0.160*	0.251**	0.308
Total	0.665	0.470	0.680	0.610	0.986

*$P < .05$.
**$P < .01$.

Table 3. Analysis of Children's Quality of Life and Alexithymia

	Difficulty in Identifying Feelings (DIF)	Difficulty in Describing Feelings (DDF)	Externally Oriented Thinking (EOT)	Total
Depressive mood	0.218**	0.336**	0.375**	0.347**
Feelings of guilt	0.383**	0.391**	0.353**	0.427**
Suicidal thoughts	0.152*	0.217**	0.184*	0.196**
Difficulty falling asleep	0.228**	0.268**	0.318**	0.305**
Shallow sleep	0.166*	0.137	0.051	0.151*
Early awakening	0.223**	0.221**	0.245**	0.289**
Impairment in work and interests	0.328**	0.293**	0.302**	0.353**
Sluggishness	0.293**	0.309**	0.262**	0.323**
Restlessness	0.258**	0.242**	0.212**	0.254**
Mental anxiety	0.145*	0.149*	0.185*	0.16*
Somatic anxiety	0.308**	0.347**	0.367**	0.389**
Gastrointestinal symptoms	0.265**	0.297**	0.352**	0.343**
General physical symptoms	0.297**	0.233**	0.257**	0.293**
Sexual symptoms	0.296**	0.275**	0.312**	0.332**
Hypochondria	0.199**	0.188*	0.276*	0.241**
Weight loss	0.344**	0.364**	0.268**	0.353**
Insight into one's own condition	0.309**	0.329**	0.279**	0.325**
Total	0.851**	0.887**	0.883**	0.981**

*$P < .05$.
**$P < .01$.

Furthermore, it is worth noting that each dimension of alexithymia demonstrates a substantial correlation with multiple dimensions of depression in children($r < 0.04$, $P < .05$). This underscores a statistically significant and robust association between alexithymia and the various aspects of depression in children, substantiating the noteworthy impact of all dimensions of alexithymia on their overall well-being.

Analysis of the Relationship between Somatic Symptoms and Alexithymia

Through the analysis of Table 4, the data reveals a significant correlation between the total scores of Somatic Symptoms and Alexithymia in children, ($r = 0.156$, $P < .05$). This positive correlation suggests that higher levels of alexithymia are closely associated with increased overall somatic symptoms in children.

Table 4. Correlation between Somatic Symptoms and Alexithymia in Children

	Pain/Weakness Symptoms	Cardiovascular and Other Symptoms	Functional Neurological Symptoms	Gastrointestinal Symptoms	Total
DIF	0.168*	0.141	0.170*	0.144*	0.175*
DDF	0.162*	0.175*	0.175*	0.097	0.183*
EOT	0.152*	0.081	0.140	0.149*	0.139
total	0.143	0.114	0.170*	0.122	0.156*

EOT, externally oriented thinking; DDF, difficulty in describing feelings; DIF, difficulty in identifying feelings.
*$P < .05$.

Further examination of the data highlighted the interrelationship between most dimensions of somatic symptoms and alexithymia. Notably, the dimension of difficulty in identifying feelings (DIF) in alexithymia demonstrates a strong correlation with all dimensions of somatic symptoms (all $P < .05$). Conversely, externally oriented thinking (EOT) in alexithymia exhibits a notably strong correlation specifically with the pain/weakness symptoms and gastrointestinal symptoms dimensions of somatic symptoms (all $P < .05$).

These findings provide valuable insights into the complex association between alexithymia and somatic symptoms. They suggest that individuals who struggle with identifying their own emotions (DIF) are likely to experience various forms of somatic symptoms across different dimensions.

Regression Analysis of Alexithymia, Somatic Symptoms, and Depression in Children with Severe Bronchial Asthma

This study employed multiple linear regression analysis (Enter method) to explore the relationship between the depression as the dependent variable and the total scores of alexithymia and somatic symptoms as independent variables in children with severe bronchial asthma. Before performing multiple linear regression, we conducted a preliminary test on the data to ensure that it satisfies the basic assumptions of multiple linear regression. We have taken these characteristics into account and adopted corresponding statistical methods in the analysis to ensure the reliability and validity of the analysis.

The results, as depicted in Table 5, total somatic symptoms vs alexithymia ($r = 0.166$, $P = .013$ vs. $r = 0.767$, $P < .001$). This suggests that somatic and alexithymia have a significant positive association with depression in children with severe bronchial asthma.

These findings emphasize the importance of considering the role of somatic and alexithymia in understanding the impact on children's depression. The significant association between somatic, alexithymia, and depression highlights the need for interventions targeting emotional awareness and expression to enhance the overall well-being and quality of life among children.

Table 5. Regression Analysis Results for the Factors Affecting Health Utility Value

	Unstandardized Coefficients		Standardized Coefficients		
	B	SE	Beta	*t*	*P*
Constant	−12.392	0.629	–	−19.698	.000***
CSI	0.097	0.038	0.166	2.513	.013*
TAS-20	0.758	0.065	0.767	11.647	.000***

$R^2 = 0.843$, $F = 496.154$.
*$P < .05$.
***$P < .001$.

Discussion

The present study aimed to explore the relationship between depression and severe bronchial asthma in children, focusing on the impact of alexithymia and somatic symptoms. The researchers sought to understand how these factors impact depression of this population. According to the results, the prevalence of mental diseases in 186 children with bronchial asthma was 16.67%, accounting for 31 cases. Data from the *National Blue Book on Depression* (published 2022-2023), which states that the prevalence of depression among adolescents is about 15-20%. In our study, the prevalence of psychiatric disorders in the 186 children with bronchial asthma is in line with the national level. Compared with the 1.1% depression rate of the general population, this incidence is significantly higher, which undoubtedly further aggravates their mental burden.[14]

It has been recognized that individuals with chronic physical illnesses may be at an increased risk for developing depression due to the significant impact of their condition on various aspects of their lives.[15-16] Numerous studies have investigated the relationship between childhood asthma and depression, aiming to establish a better understanding of the complex interplay between these 2 conditions. This analysis demonstrated that children with severe bronchial asthma experience more severe depression compared to the general population in China. In addition to the physical symptoms of asthma, the psychological factors such as somatic symptoms and alexithymia play a significant role in determining their overall well-being. Therefore, it is crucial to address both the physical and emotional aspects to improve the well-being and quality of life outcomes of children with severe bronchial asthma.

The higher levels of physical symptoms observed in children with severe bronchial asthma are consistent with previous studies in children with chronic diseases.[17,18] Notably, this population has a more severe burden of somatic symptoms (grade II) compared to mild or mild symptoms (grade 0 or grade I). Alexithymia can affect coping mechanisms and social interactions. Although there is limited research on alexithymia in this particular population, studies in other clinical populations have shown that Alexithymia still has a negative impact on quality of life,[19-23] and healthcare professionals need to consider incorporating emotional processing in the management of respiratory diseases in children into the medical model.

In this study, the presence of alexithymia, as assessed using the TAS-20 scores, was found to be significantly associated with depression in children. This suggests that difficulty in identifying and expressing emotions has a profound impact on their daily functioning and subjective

well-being. The strong correlations observed between each dimension of alexithymia and multiple dimensions of depression underscore the comprehensive nature of emotional difficulties experienced by these children. Interventions that promote emotional awareness, expression, and coping strategies may be crucial in improving symptoms of childhood depression. Moreover, the present study found that somatic symptoms were significantly correlated with depression in children with severe bronchial asthma. This suggests that the presence and severity of somatic symptoms have a direct impact on various aspects of daily functioning and well-being. Importantly, the study identified a significant positive correlation between somatic symptoms and alexithymia in children with severe bronchial asthma. Higher levels of alexithymia were closely associated with increased overall somatic symptoms. Specifically, the DIF dimension of alexithymia demonstrated a strong correlation with all dimensions of somatic symptoms, while EOT exhibited notable correlations with pain/weakness symptoms and gastrointestinal symptoms. The positive correlation between somatic symptoms and alexithymia further supports the interplay between physical and emotional factors in this population.

The psychological challenges faced by children with chronic respiratory diseases remain a significant concern. Within this demographic, children often grapple with heightened physical pain and discomfort, rendering them more emotionally vulnerable than their peers. The potential for increased anxiety, depression, and even diminished self-esteem poses obstacles to their typical psychological development. Moreover, the persistent burden of chronic respiratory diseases subjects these children to frequent medical examinations and treatments, intensifying their psychological strain.

The impact of psychological disorders on the health and overall quality of life for children with chronic respiratory diseases is profound. Beyond affecting academic performance and social relationships, these psychological challenges may further exacerbate their physical conditions. In the long term, this intricate interplay between physical and psychological factors can contribute to a detrimental cycle. Therefore, delving deeply into the study and resolution of mental disorders in children with chronic respiratory diseases holds immense significance.

By thoroughly analyzing the root causes of these psychological challenges, tailored interventions such as psychological support and treatment can be designed to assist children in effectively coping with the emotional pressures brought about by their diseases. This approach not only aims to alleviate the psychological burden but also strives to enhance their overall quality of life. Timely interventions and psychological support can significantly contribute to improving their sense of well-being. Furthermore, these measures can positively impact the child's recovery process, facilitating better management and control of the symptoms associated with chronic respiratory diseases.

While this study offers valuable insights into the impact of somatic symptoms and alexithymia on depression in children with severe bronchial asthma, it is essential to acknowledge certain limitations. Firstly, the cross-sectional study design employed here restricts the establishment of causal relationships between variables. To gain a more comprehensive understanding of the sequence of somatic symptoms, alexithymia, and depression over time, future research should prioritize longitudinal studies. Secondly, the small sample size in this study may limit the generalizability of findings due to the specific characteristics of the study sample. Ensuring broader applicability requires future studies to encompass larger and more diverse samples. Additionally, enhancing the reliability of results can be achieved by incorporating objective measures and obtaining insights from multiple informed sources, such as parents and teachers and baseline information on family history and so on. This multifaceted approach will contribute to a more thorough comprehension of the impact of somatic symptoms and alexithymia on depression in children with severe bronchial asthma.[24-26]

In conclusion, this study delves into the impact of alexithymia and somatic symptoms on the well-being and quality of life in children with severe bronchial asthma. The findings reveal an elevated risk of depression within this specific population, contributing to an increased psychological burden. Children grappling with severe bronchial asthma are more susceptible to experiencing severe depression compared to the general population. Effectively addressing both the physical and emotional challenges faced by this group is paramount for enhancing their overall well-being. Psychological factors, including somatic symptoms and alexithymia, play a crucial role in shaping their overall sense of well-being. Therefore, adopting an integrated approach that acknowledges and addresses their physical and emotional needs is crucial for improving the quality of life for children dealing with severe bronchial asthma.

Availability of Data and Materials: *The data that support the findings of this study are available from the corresponding author upon reasonable request.*

Ethics Committee Approval: *This study was approved by the Ethics Committee of Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine (Approval No: 2023-115, Date: October 8, 2023).*

Informed Consent: *Informed consent was obtained from the parents of children who agreed to take part in the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – C.D.; Design – C.D.; Supervision – C.D.; Resources – C.D.; Materials – D.S., L.L., Y.F., L.Z.; Data Collection and/or Processing – D.S., L.L., Y.F., L.Z.; Analysis and/or Interpretation – D.S., L.L., Y.F., L.Z.; Literature Search – D.S., L.L., Y.F., L.Z.; Writing – C.D., D.S.; Critical Review – C.D., D.S.*

Declaration of Interests: *The authors have no conflicts of interest to declare.*

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