

Probiotics: A Possible Preventative Measure of Atopic Asthma?

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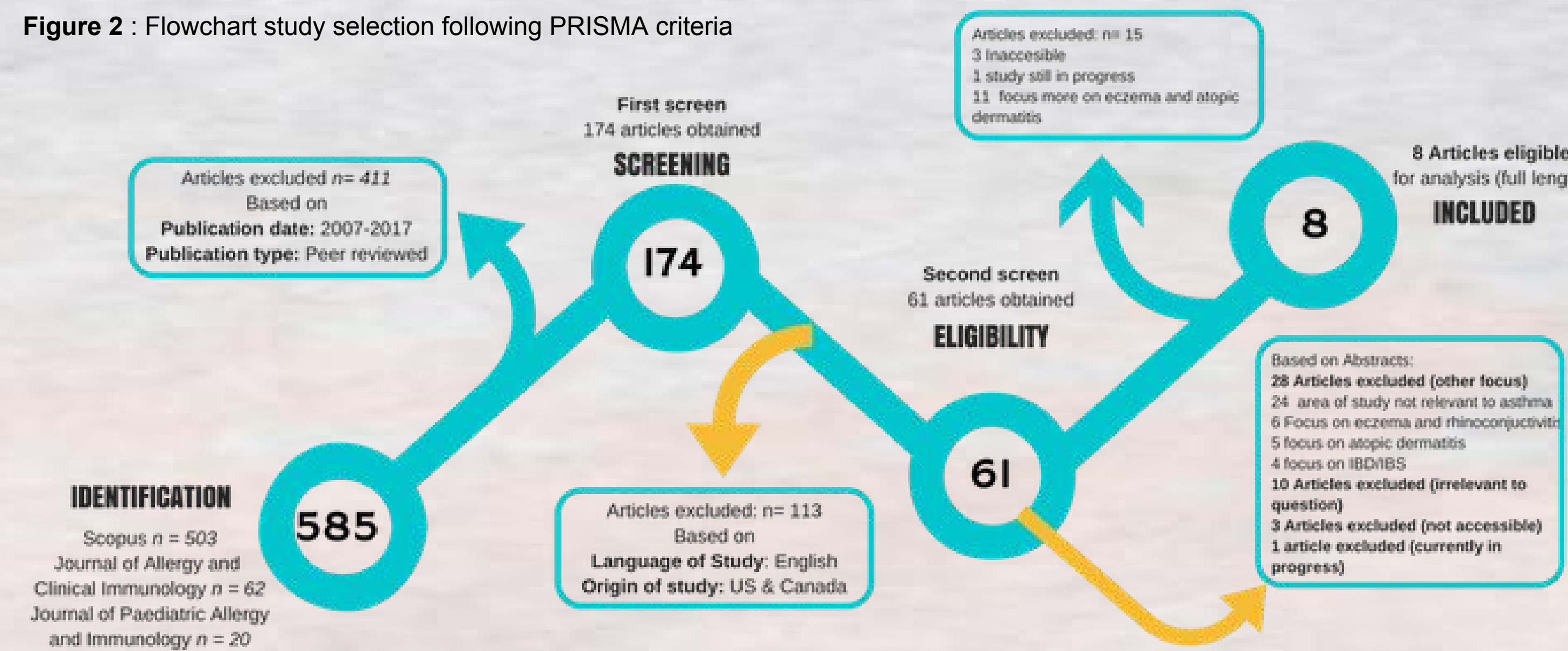
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ABSTRACT

Introduction: Asthma is a chronic inflammatory immune disorder characterized by acute episodes of bronchial hyper responsiveness. This is caused by recurrent dysregulation of several immunoregulatory proteins such as interleukins, cytokines, clusters of differentiation, and immunoglobulins. In Canada and the U.S, the risks of developing atopic asthma can range from 1 case in every 10 children (general population), to 1 case in every 5 children (high-risk populations: African American descent). Asthma has an incidence rate of 8.5 million cases each year while the prevalence is 161.3 cases /1000 person years, depending on the population and environment studied. Children with decreased microbial exposure were observed to develop an altered gut microbiota leading to a higher risk for the development of asthma and allergic diseases. **Objective:** The aim of this review is to examine if probiotics decrease the risk of developing atopic asthma in children with an abnormal gut microbiome. **Methodology:** Concepts pertaining to the research question were identified and expanded upon through keywords: risk, and asthma or immune function, and probiotics or gut microbiome. Peer reviewed journals published between the years 2007-2017, from Canada and/or U.S.A were examined. Exclusion criteria included terms relating to airway, throat and respiratory microbiota to eliminate articles irrelevant to the focus of this study. The search strategy was developed on PubMed and adapted to Scopus, Journal of Allergy and Clinical Immunology and Journal of Pediatric Allergy and Immunology to yield the most relevant research articles. This resulted in 61 articles, from which 8 relevant articles were deemed eligible for the making of this literature review. **Results:** The 8 most relevant studies consisted of 2 systematic reviews and meta-analyses (one being meta-analysis only), 2 prospective nested case-control studies, and only 1 cohort and RCT each. The RCT study showed a positive correlation between the administration of probiotics and the reduction of asthma onset, while all three case-controls and cohorts listed an altered gut microbiota as a causative risk factor for developing asthma. Lastly, the 2 systematic reviews and meta-analyses concluded that no clinically-relevant association was present between the administration of probiotics and the prevention of asthma development. **Conclusion:** Due to the large heterogeneity of results, little compiled evidence supports a relation between the delivery of probiotics and the prevention of asthma development as of yet. Studies more specific to probiotics in relation to asthma development in larger cohorts need to be conducted to better understand any possible associations.

METHODOLOGY

Figure 2 : Flowchart study selection following PRISMA criteria



- A search strategy for this literature review was developed on PubMed and adapted to 3 databases: Scopus, Journal of Allergy and Clinical Immunology & Journal of Pediatric Allergy and Immunology
- Key words pertaining to research objective were used: Risk AND Asthma OR Immune Function AND Gut Microbiome OR Probiotics - Findings were narrowed to publication dates ranging from 2007-2017.
- Non-peer reviewed journals, studies outside of the English language and performed outside of Canada and U.S were omitted
- Exclusion criteria terms included: Airway, Throat and Respiratory microbiota to yield articles most relevant to asthma
- This methodology resulted in 61 potential articles - the abstracts of which were used to determine eligibility of studies for this review
- Through this 21 full-length articles were further analysed and 8 articles that met the predefined criteria were selected in the making of this literature review.

RESULTS

Table 1: Results and characteristics of structured literature review

Study No. (Authors)	Type of Study	No. Participants or publications and Population studied	Database/Intervention/Assessment	Outcome/Conclusion
1 - Azad, M. B. (2013)	Systematic review and meta-analysis (double blind placebo controlled trials)	Population: 20 RCTs (Total of 4866 infants in first year of life) 14 trials: Participants of high asthma risk, remaining 6 trials in unselected populations.	Database: Medline, Embase, and Central (Cochrane library). Intervention: Multiple probiotic organisms in isolation or combination given between 1-25 months (Dose range from 10 ⁸ - 10 ¹¹ colony forming units) Assessment: Physician diagnosed asthma and wheeze	Incidence of diagnosed asthma was 11.2% - probiotics, and 10.2% - placebo. Of the 3257 infants enrolled in 9 trials contributing to asthma data, the risk ratio of doctor diagnosed asthma in participants randomized to receive probiotics was 0.99 (95% CI, I ² =0). The risk ratio of incident wheeze was 0.97 (I ² =0). Risk ratio of lower respiratory tract infections came to be was 1.26 (I ² =0). No evidence found to support a protective association between supplementation of probiotics and doctor diagnosed asthma of childhood wheeze.
2 - Elazab, N. (2017)	Meta-analysis	25 total studies: Double-blinded, randomized, placebo-controlled trials which studied children from birth to 18 years.	Database: Medline, Highwire, Cumulative Index to Nursing and Allied Health Literature, Web of Knowledge, and Intervention: Administered bacterial probiotics (single strain or mixture) prenatally and postnatally within first year of life. Assessment: Random effects model and meta-regression.	Probiotics had a mean reduction of -7.59 U/mL in IgE. RR of atopic sensitization was significant 0.88 (P=0.035). Probiotics did not significantly reduce development of asthma or wheeze, RR= 0.96 (95% CI) during infancy. Length of follow up modified the effect of probiotics on total IgE levels- decrease in levels more pronounced with longer follow-up.
3 - Cabana, M. (2017)	RCT	92 subjects (infants) till 5 years of age.	Intervention: Infants received a daily dose of 10 billion colony-forming units of LGG and 225 mg of inulin	Cumulative risk of asthma at 5 years was 17.4% in the control group and 9.7% in the LGG group, but no significant risks were reduced at 2 years of age.
4 - Mikael, K. (2009)	RCT (double-blinded, placebo controlled study)	1223 mothers with infants at high risk for allergy	Intervention: administration of probiotic mixture and placebo to mothers in last month of gestation, and pro + probiotics to infants until the age of 6 months. Assessments: Results collected at 5-year visit.	Frequencies of allergic disease and sensitization in the probiotic and placebo groups were similar: 52.6% vs. 54.9%. No difference in frequency of asthma (13.0% vs. 14.1%) in both groups.
5 - Rose, M. A. (2010)	RCT	131 randomly assignment children (6-24 months old).	Intervention: administration of <i>Lactobacillus rhamnosis</i> (LGG, 10 ¹⁰ colony forming units) or placebo	Fewer sensitizations towards aeroallergens after 6 months of LGG (P=0.027) and after 6 months of follow-up (P=0.03). Overall oral LGG had no clinical effect on asthma-related events and only mild positive effects on allergic sensitization.
6 - Fujimura, K. (2016)	Cohort	298 subjects from 1-11 months old children. Pregnant women and between the ages of 21 and 49 and their infants were recruited.	Assessment: Stool samples and 16s rRNA sequencing was used to determine which main strains exist.	The highest risk group to develop multi-sensitized atopy had a lower relative abundance of certain bacteria and an observed fetal metabolome enriched with pro-inflammatory metabolites.
7 - Arrieta, M. et al. (2015)	Prospective nested case-control	319 subjects (young children) enrolled in the CHILd study.	Assessments: Used Asthma Predictive Index (API), qPCR and 16s at 3 months and 1 year. Urine metabolomics were also used. Intervention: FLVR (<i>Faecalibacterium</i> sp., <i>Lachnospira</i> sp., <i>Veillonella</i> sp., and <i>Rothia</i> sp.) were supplemented to case studies.	In the asthmatic case group, urine metabolites influenced by bacterial metabolism were excreted differently, as well as decreased concentrations of acetate. Murine FLVR supplementation was observed to reduce concentrations of proinflammatory cytokines (IFN-γ), tumor necrosis factors (TNF), and interleukins 17A & 6.
8 - Stiemsma, L. T. (2016)	Prospective nested case-control	286 subjects (infants) followed infants from pregnancy to 5 years of age, from the CHILd study.	Assessment: Microbial community analysis- using 16S rRNA extraction, PCR amplification, and bioinformatics to assess bacterial populations in stool samples at 3 months and 1 year.	At 3 months asthmatic subjects were colonized with 1/5 less <i>Lachnospira</i> and 31 times more C. neonatae. At 3 months, OR of developing asthma decreases as the ratio of L/C increases, OR= 15 > 1.0 > 0.37 > 0.44, suggesting a protective effect against asthma development with the increase of L/C ratio

Table 2: Article Quality Assessment

Criteria	1	2	3	4	5	6	7	8
High degree of methodology description	O	O	X	O	O	O	O	O
Adequate sample size	O	O	X	O	O	O	X	O
High degree of population and intervention description	O	O	O	O	O	O	O	O
Precise definition of outcome	O	O	O	O	O	O	X	O
Total	4/4	4/4	2/4	4/4	4/4	4/4	2/4	4/4

X= Did not meet criteria
O= Met criteria

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DISCUSSION

Results from article interpretations answered three questions relative to gut microbiota dysbiosis, probiotics, and asthma development.

- ✓ **How is microbiome dysbiosis related to the development of asthma? (3/8 studies)**
 - Highest risk groups for asthma development had a lower abundance of certain gut bacteria.
 - Persons with asthma had a higher blood count of proinflammatory metabolites as well as an impacted excretion rate of other metabolites (urobilinogen) and sulfated bile acids.

Evidence that asthmatics had the most abnormalities in gut microbiota and bacterial metabolites.
- ✓ **How does probiotic administration affect immune function? (2/8 studies)**
 - A mean reduction of immunoglobulin E levels was observed as well as IgE related allergic diseases. Elevated IgE levels are related to allergic diseases, inflammation, immunodeficiency, and more.
 - A reduction of proinflammatory cytokines (IFN-γ), tumor necrosis factors (TNF), and interleukins 17A & 6.

Evidence that probiotics can reduce proinflammatory cytokines as lead to less inflammation and hypersensitivity.
- ✓ **How does probiotic administration influence asthma reduction? (4/8 studies)**
 - Similar rates of asthma diagnosis were observed between patients receiving probiotics and patients receiving the placebo at 25 months.
 - No significant evidence of asthma reduction at 6 months and 2 years.
 - Bacterial strains like LGG and L/C showed a decreased risk of asthma development at 5 years.

Probiotics show no effect on asthma reduction in the short-term, but may have a protective and preventative effect in the long term. More research required for a conclusive outcome.

LIMITATIONS

- Only articles written in English were included resulting in a foreign language bias.
- Only a few studies indicated that a link exist between probiotic use and asthma development.
- Most of the studies required larger sample sizes
- Type 2 errors (False-negative) observed in a systematic review and prospective case control study.

STRENGTHS

Our literature review made use of RCTs, systematic reviews and meta-analysis which forms the basis of the highest level of clinical evidence.

Eligible articles for this study were independently assessed by 3 reviewers and discrepancies resolved through consensus to assess the quality of each study to minimize the risk of selection bias. Used a predetermined methodological approach each paper for selection process.

FUTURE IMPLICATIONS/ RECOMMENDATIONS

- Asthma continue to remain one of the most prevalent childhood disease worldwide, where risk factors such as the alteration of gut microbiota have been identified. However the current available literature does not conclusively identify probiotics as a possible solution in preventing asthma.
- Given that probiotics are a comparatively cheaper and preventive option, more randomized trials need to be conducted in order to establish a clear link between probiotics and asthma
- Based on the results of a few studies, more research should also focus on the specific lacking bacteria in the specific role of lacking bacteria in the development of asthma, and possibly use them as clinical diagnostic markers for early asthma onset.

CONCLUSION

The majority of the findings indicated in this literature review suggests that there is no link between probiotic intake and primary prevention of asthma development. However, there is not much available information or research about the link between the outlined variables. Thus, more research is necessary before probiotic use on asthma treatment is dismissed.

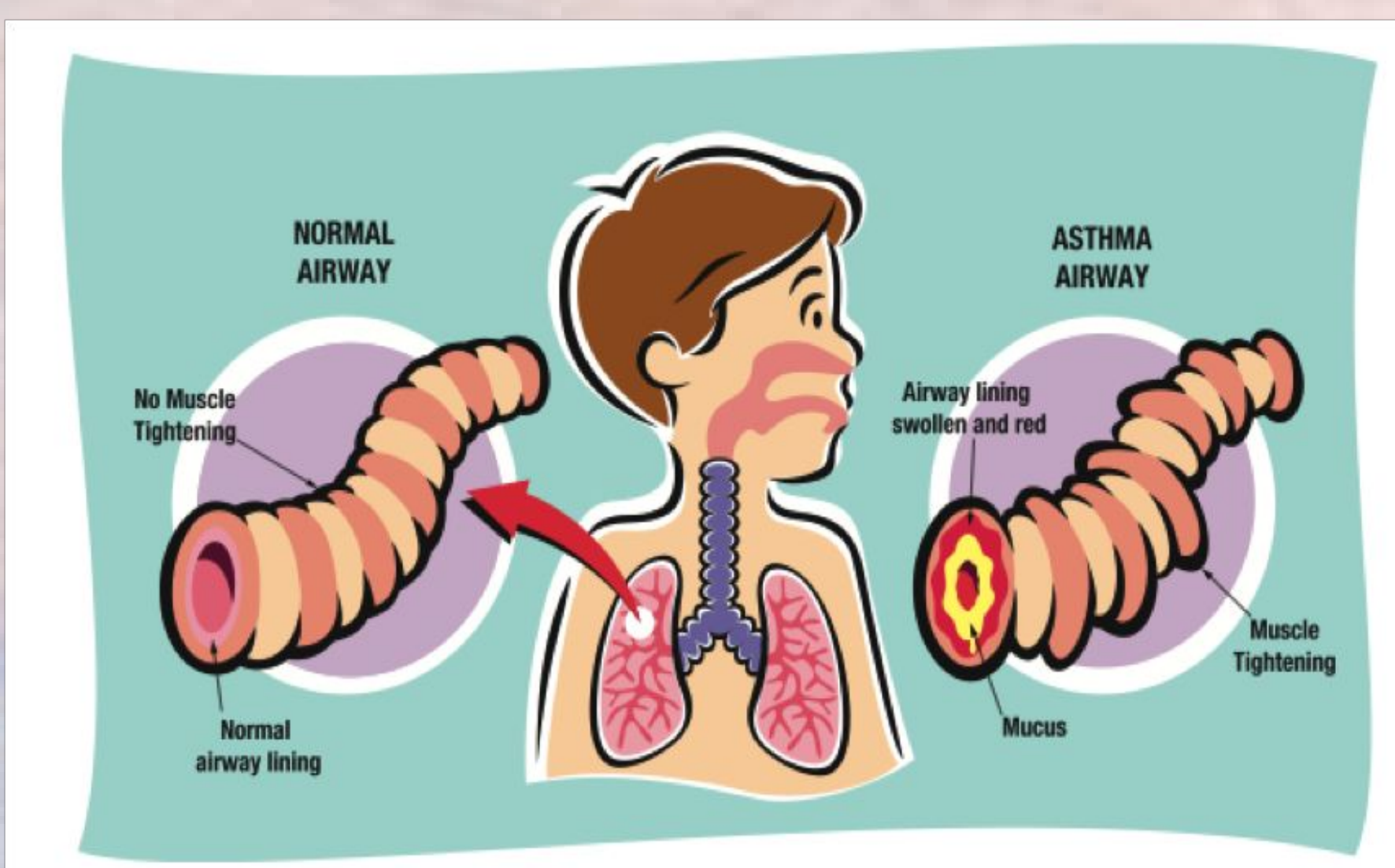


Figure 1: Asthma in children