Received: 19 September 2021 | Accepted: 12 January 2022

DOI: 10.1002/ppul.25828

ORIGINAL ARTICLE: ASTHMA

WILEY

Factors associated with resolution of childhood asthma by the age of 17: Large cohort analysis

Shmuel Goldberg MD[1] | Elie Picard MD[1] | Leon Joseph MB, ChB[1] | Ron Kedem PhD[2] | Adir Sommer MD[2] | Dorit Tzur MA[2] | Shlomo Cohen MD[1]

[1]Institute of Pediatric Pulmonary Medicine, Shaare Zedek Medical Center, Jerusalem, Israel

[2]Medical Corps, Israel Defense Forces, Tel Hashomer, Israel

Correspondence
Shmuel Goldberg MD, Institute of Pediatric Pulmonology, Shaare Zedek Medical Center, P.O.B. 3235, Jerusalem 91301, Israel.
Email: sgoldberg@szmc.org.il

Abstract

Background: Many children with asthma will become asymptomatic during adolescence. In this study, we evaluated factors associated with recovery from asthma by the age of 17.

Methods: The medical records of 17-year-old conscripts to the Israeli army with asthma were compared with the records of conscripts with rigorously diagnosed resolved asthma. We assessed the association between the following parameters and asthma resolution: body mass index (BMI), recurrent rhinitis, birth season, socioeconomic level, and cognition.

Results: Sixty-eight thousand and ninety conscripts with active asthma were compared to 14,695 with resolved asthma. In univariate analysis, rhinitis, overweight, underweight, higher socioeconomic level, and lower cognitive score were associated with active asthma ($p < 0.001$ for both sexes), but not the season of birth. In multivariate analysis, only overweight, underweight, rhinitis, and lower cognitive score ($p < 0.001$ for both sexes) remained significantly associated with persistence of asthma.

Conclusions: Although association does not prove causation, our finding is another reason to encourage adolescents with asthma to maintain a normal body weight. Prospective interventional studies are needed in order to decide whether changing weight to ensure BMI is within the ideal range and controlling rhinitis increases the odds of resolution of asthma in adolescence.

KEYWORDS

birth season socioeconomic status, BMI, cognition, overweight, resolution of asthma, rhinitis, underweight

Shmuel Goldberg and Elie Picard contributed equally to this study.

1 | INTRODUCTION

Many children with asthma become asymptomatic during adolescence or early adulthood,[1,2] yet more than half of asymptomatic patients will continue to have impaired pulmonary function tests or evidence of bronchial hyperactivity.[3] Risk factors for unremitting asthma include severe asthma, being female, family history of asthma,[2] early onset of puberty, active sinusitis, skin test allergic sensitization,[1] and history of atopy.[4] Rhinitis was also found to be related to the persistence of asthma.[5] By contrast, male gender, milder disease,[6] lower initial bronchial hyperreactivity, greater gain in small airways function,[7] early-onset asthma, and living in a rural and medium urban location[4] are associated with resolution of asthma.

Identifying factors that influence recovery from asthma might shed light on the pathophysiology of the disease. In addition, the presence of risk factors for unremitting asthma may influence therapeutic decisions.

Yet, only a few of the risk or protective factors are modifiable after the diagnosis has been made. One potential factor is overweight. Although overweight is associated with asthma,[8] very few studies have examined the effect of being overweight on the chances of recovering from asthma.[6,7,9]

The purpose of this study was to reevaluate factors associated with full recovery from asthma in a large cohort of 17-year-olds.

2 | PATIENTS AND METHODS

We reviewed the medical records of 1,080,564 consecutive 17-year-old male and female potential conscripts to the armed forces of Israel (Israel Defense force [IDF]) born between 1978 and 1999, searching for individuals with a current or past history of asthma. We examined the relationship between resolution of asthma and body mass index (BMI), recurrent rhinitis, birth season, socioeconomic level, and cognition. The reason for choosing these specific parameters is their known role as risk factors for the development of asthma.[5,8,10–12] Other relevant factors including smoking were not included in the database and could not be analyzed.

The diagnosis of asthma or history of asthma was made by a military physician on the basis of the following data: a medical questionnaire filled by the conscript, a letter submitted by the primary care physician (PCP), clinical interview, use of asthma medications, and physical examination. Baseline spirometry was performed by all conscripts in whom the PCP indicated a current or previous history of asthma. In addition, an exercise challenge, with or without methacholine challenge testing, was performed. The challenge tests were performed according to the American Thoracic Society Guidelines.[13] Conscripts were assigned a diagnosis of "resolved asthma" if the PCP documented asthma more than 3 years before the evaluation, and if the conscript reported that there were no symptoms and no use of asthma medications for the last 3 years. In addition, asthma was considered resolved only if the physical examination on the day of the evaluation, the spirometry, and the challenge test were normal. Current asthma was diagnosed in individuals who had at least one episode of asthma symptoms in the 3 years before evaluation or had an abnormal physical examination, pulmonary function test, or a positive challenge test.

A diagnosis of recurrent rhinitis was assigned if the questionnaire completed by the PCP indicated frequent clinic visits due to rhinitis. Birth season was defined according to the local climate as follows: winter (December through February), spring (March through May), summer (June through August), and fall (September through November). In addition, every conscript performs a battery of cognitive tests as part of routine evaluation. These tests yield a cognitive score that is equivalent to a normally distributed intelligence quotient.[14]

The socioeconomic level was determined by scoring each individual's residential address. Each area was assigned a score ranging from 1 (*lowest*) to 10 (*highest*) using an army protocol that we were not granted access to.

The research protocol was reviewed in its entirety and approved by the Ethics Committee of the IDF medical corps.

2.1 | Statistical analysis

The association between resolved asthma and rhinitis, overweight, underweight, season of birth, and socioeconomic level was assessed using the χ^2 test. The association between resolved asthma and cognitive score was assessed using Student's t test. A p value lower than 0.05 was considered statistically significant. A multivariate analysis was performed defining persistent asthma as the dependent variable, and recurrent rhinitis, overweight, underweight, season of birth, socioeconomic level, and cognitive score as independent variables. Odds ratios (OR) and 95% confidence intervals (95% CIs) were calculated.

3 | RESULTS

A total of 82,785 adolescents were included in the study, of which 53,893 were males (65%) and 28,892 were females (35%). Of the males, 41,813 (77.6%) had active asthma and 12,080 (22.4%) had resolved asthma. Of the females, 26,277 (90.9%) had active asthma and 2615 (9.1%) had resolved asthma. In univariate analysis (Table 1a and Table 1b), the prevalence of rhinitis, overweight, and underweight were higher in both males and females with active asthma compared with individuals with

TABLE 1a The association between recurrent rhinitis, BMI, season of birth, socioeconomic level, and cognitive score with resolution of asthma in males

	Univariate analysis—males		
	Active asthma (n = 41,813)	Resolved asthma (n = 12,080)	p value
Rhinitis, number of participants (%)			
Yes	14,976 (35.8)	1838 (15.2)	<0.00001
No	26,837 (64.2)	10,242 (84.8)	
BMI, number of participants (%)			
<19	7640 (18.4)	1863 (15.5)	<0.00001
19–25	26,829 (64.6)	8311 (69.2)	When comparing normal to both low and high BMI
>25	7077 (17.0)	1838 (15.3)	
% with abnormal BMI	35.4	30.6	
Birth season, number of participants (%)			
Winter	9805 (23.4)	2911 (24.1)	0.09
Spring	9995 (23.9)	2795 (23.1)	When comparing all the seasons together
Summer	11,071 (26.5)	3133 (25.9)	
Fall	10,942 (26.2)	3241 (26.8)	
Socioeconomic level, number of participants (%)			
1–3 (lowest)	1093 (2.7)	355 (2.9)	<0.00001
4–6	17,671 (43.2)	5575 (46.3)	
7–10	22,979 (54.1)	6111(50.8)	
Cognitive score, mean ± SD	111.3 ± 16.5	112.0 ± 16.4	<0.001

Note: The absence of rhinitis, normal BMI, and higher cognitive score are associated with the resolution of asthma. The highest socioeconomic level is associated with the persistence of asthma. Some variables were missing in some of the participants.

Abbreviation: BMI, body mass index.

resolved asthma. Individuals residing in areas of higher socioeconomic level were also more likely to have active asthma. The cognitive score was slightly but significantly lower in individuals with active asthma. The season of birth was similar in both groups. After multivariate analysis, the association of persistent asthma with overweight, underweight, rhinitis, and lower cognitive score remained significant ($p < 0.001$), while the association with socioeconomic area level lost its statistical significance (Table 2).

4 | DISCUSSION

We found that adolescents with active asthma had higher rates of overweight, underweight, and rhinitis, and a slightly, but significantly, lower cognitive score compared with adolescents who recovered from asthma. A relationship to socioeconomic status was seen in univariate analysis, but not in multivariate analysis.

4.1 | BMI and persistence of asthma

4.1.1 | Overweight

The OR for active asthma was significantly higher in overweight adolescents compared with adolescents with normal weight and reached 1.24 in males and 1.39 in females. The association between overweight and asthma is well known;[9] however, few studies have looked at the association between weight and the resolution of childhood asthma. We found a single study[6] that reported that obesity at age 11 in asthmatics was associated with an increased OR for persistent asthma of 5.2–8.9 depending on the severity of asthma. Other studies did not find such a relationship.[7,9]

Several possible mechanisms could explain the association between overweight and asthma. One possibility is shared inflammatory processes. Another possibility is that having asthma leads to inactivity and secondary obesity. Another possible mechanism includes the mechanical effect of obesity on the airways.[15]

TABLE 1b The association between recurrent rhinitis, BMI, season of birth, socioeconomic level, and cognitive score with resolution of asthma in females

	Univariate analysis—females		
	Active (*n* = 26,277)	Resolved asthma (*n* = 2615)	*p* value
Rhinitis, number of participants (%)			
Yes	7576 (28.8)	318 (12.1)	<0.00001
No	18,701 (71.2)	2297 (77.9)	
BMI, number of participants (%)			
<19	4514 (17.6)	382 (14.8)	<0.00001
19–25	16,829 (65.7)	1849 (71.7)	
>25	4276 (16.7)	348 (13.5)	
% with abnormal BMI	34.3	28.3	
Birth season, number of participants (%)			
Winter	6156 (23.4)	650 (24.9)	0.16
Spring	6543 (24.9)	673 (25.7)	
Summer	7000 (26.6)	662 (25.3)	
Fall	6578 (25.0)	630 (24.1)	
Socioeconomic level, number of participants (%)			
1–3 (lowest)	250 (0.9)	26 (1.0)	<0.00001
4–6	10,939 (37.9)	1296 (49.6)	
7–10	15,049 (52.2)	1289 (49.4)	
Cognitive score, mean ± SD	108.7 ± 14.9	110.3 ± 15.0	<0.001

Note: The absence of rhinitis, normal BMI, and higher cognitive score are associated with the resolution of asthma. The highest socioeconomic level is associated with the persistence of asthma. Some variables were missing in some of the participants.

Abbreviation: BMI, body mass index.

An important practical question is whether intentional weight loss would increase the chance of asthma resolution. Studies in adults[16–21] and in children[22] have shown that weight loss reduces the severity of asthma, but did not investigate the possibility of complete resolution of asthma. Since weight loss improves the severity of asthma, and because of the other general benefits of maintaining a normal body weight, overweight adolescents with asthma should be encouraged to reduce weight. They can be cautiously told that weight loss may have the potential to reduce the chance of asthma persisting into adulthood.

4.1.2 | Underweight

The OR for active asthma was significantly higher in underweight adolescents compared with adolescents with normal weight and reached 1.31 in men and 1.27 in women. Few studies have evaluated the effect of being underweight on the risk for asthma, although a recent study from Korea showed an increased risk of asthma in underweight males but not in females.[23] Another study[11] showed a prevalence of asthma in underweight adults that was higher than expected. Low weight has also been reported to be associated with poor asthma control.[24,25] We did not find studies other than the current one, examining the association between low BMI and asthma resolution.

4.2 | Rhinitis and persistence of asthma

The positive association between rhinitis and the persistence of asthma was highly significant with an OR of 3.16 in males and 2.98 in females. We do not have data regarding the etiology of the rhinitis, but it can be assumed that it was allergic in most cases.[26–28] The association between allergy and persistent asthma was reported in a previous systematic review.[5] The plausible explanation is TH_2 activity, which manifests in both allergic rhinitis and in childhood asthma. It has yet to be determined whether controlling rhinitis influences the likelihood of recovery from asthma.

TABLE 2 The association between BMI, recurrent rhinitis, and socioeconomic level with resolution of asthma—multivariate analysis

	Males (n = 51,046) Active asthma = 39,632 Resolved asthma = 11,414		Females (n = 26,742) Active asthma = 24,298 Resolved asthma = 2444	
Multivariate analysis	OR for persistent asthma	p value	OR for persistent asthma	p value
BMI				
<19	1.31 (1.39–1.23)	<0.001	1.27 (1.43–1.13)	<0.001
19–25	1		1	
>25	1.24 (1.22–1.26)	<0.001	1.39 (1.34–1.45)	<0.001
Rhinitis				
No	1		1	
Yes	3.161 (2.99–3.34)	<0.001	2.983 (2.63–3.38)	<0.001
Socioeconomic level				
1–3 (lowest)	1		1	
4–6	1.023 (0.90–1.164)	0.724	0.874 (0.575–1.330)	0.529
7–10	1.109 (0.97–1.26)	0.116	1.186 (0.779–1.806	0.426

Note: The OR for persistent asthma is higher in individuals with abnormal BMI and in individuals with chronic rhinitis. The cognitive score also remained significantly associated with asthma resolution ($p < 0.001$). The socioeconomic level is not associated with asthma resolution. Analysis was done only on participants with all variables available.

Abbreviation: BMI, body mass index; OR, odds ratio.

4.3 | Cognition and persistence of asthma

In a previous study, we reported a positive association between cognitive score and asthma.[12] In the present study, we found that the average cognitive score in individuals with resolved asthma was slightly higher than in those with active asthma. It is possible that a higher cognitive score is associated with a higher rate of diagnosis of pediatric asthma that resolves in adolescence. This may reflect a greater awareness of childhood asthma among families whose children have higher cognitive scores. It will be interesting to see if future studies will confirm our observation.

4.4 | Other variables and persistence of asthma

4.4.1 | Socioeconomic level

The low socioeconomic level has been previously described as a risk factor for severe asthma.[11] In the current study, we did not find an association between socioeconomic level and asthma resolution.

4.4.2 | Birth season

The birth season influences the odds of developing asthma with a higher risk for asthma in individuals born in the fall[10,29] or August–January.[27] In the current study, we did not find an association between birth season and resolution of asthma. We hypothesize that asthma that develops in children born in the higher risk seasons is not phenotypically different from the asthma developed in children born in other seasons, at least in regard to the chance of resolution.

4.5 | Study strengths

The main strengths of this study are the large sample size and the strict definition of active versus resolved asthma. The requirement for a negative challenge test in the definition of resolution prevented asymptomatic individuals with airway hyperactivity from being included in the resolved asthma group.

4.6 | Study limitations

The proportion of conscripts who recovered from asthma was relatively low, especially in women. It is possible that some adolescents, who suffered from mild asthma in the past, did not report these symptoms and were not included in the study population. Another limitation is the inability to separate individuals who recently developed asthma from individuals with long-lasting asthma. Our study is also limited by the lack of availability of additional clinical parameters, including smoking or the type of rhinitis. Similarly, we do not have data regarding which challenge test was used for asthma diagnosis in each conscript. That might be important due to the difference in

sensitivity and specificity between methacholine and exercise challenge tests.[30]

4.7 | Conclusion

Overweight and underweight are associated with the persistence of asthma through adolescence. This observation gives further support to the existing recommendations to maintain a BMI in the normal range throughout childhood. Physicians should be aware that rhinitis is associated with the persistence of asthma.

There is a need for interventional studies to examine whether changing weight to fall within the recommended BMI range and treating rhinitis could increase the odds for asthma resolution in adolescents.

ACKNOWLEDGMENTS

There is no funding information for this article.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Shmuel Goldberg: conceptualization (lead), formal analysis (equal), investigation (lead), methodology (lead), supervision (lead), writing—original draft (lead), and writing—review and editing (equal). **Elie Picard**: conceptualization (equal), methodology (equal), writing—review and editing (lead). **Leon Joseph**: formal analysis (equal), investigation (equal), writing—review and editing (lead). **Ron Kedem**: data curation (equal), formal analysis (lead), methodology (equal), software (equal). **Adir Sommer**: conceptualization (equal), investigation (equal), methodology (equal). **Dorit Tzur**: data curation (equal), formal analysis (equal), investigation (equal), methodology (equal). **Shlomo Cohen**: conceptualization (lead), formal analysis (lead), methodology (lead), writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

The database was created and owned by the Medical Corps. The use of the data was controlled by the research unit of the Medical Corps. We were able to perform statistical analysis, but we were not given access to any individualized data, hence we cannot share this data.

ORCID

Shmuel Goldberg http://orcid.org/0000-0003-4037-0447
Elie Picard http://orcid.org/0000-0001-6796-3459
Leon Joseph https://orcid.org/0000-0002-2891-642X
Shlomo Cohen http://orcid.org/0000-0003-0235-0779

REFERENCES

1. Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med*. 2004;1(170):78-85.
2. Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. *BMJ*. 1994; 9(309):90-93.
3. Vonk JM, Postma DS, Boezen HM, et al. Childhood factors associated with asthma remission after 30 year follow up. *Thorax*. 2004; 59:925-929.
4. Oluwole O, Rennie DC, Goodridge D, et al. The course of asthma: a population-based 10-year study examining asthma remission in children diagnosed with asthma in preschool. *Pediatr Pulmonol*. 2020;55:1924-1935.
5. Rodríguez-Martínez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Factors predicting persistence of early wheezing through childhood and adolescence: a systematic review of the literature. *J Asthma Allergy*. 2017;10:83-98.
6. Fuchs O, Bahmer T, Rabe KF, von Mutius E. Asthma transition from childhood into adulthood. *Lancet Respir Med*. 2017;5: 224-234.
7. Arshad SH, Raza A, Lau L, et al. Pathophysiological characterization of asthma transitions across adolescence. *Respir Res*. 2014;15:153.
8. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med*. 2007;175:661-666.
9. Covar RA, Strunk R, Zeiger RS, et al. Predictors of remitting, periodic, and persistent childhood asthma. *J Allergy Clin Immunol*. 2010;125: 359-366.
10. Gazala E, Ron-Feldman V, Alterman M, Kama S, Novack L. The association between birth season and future development of childhood asthma. *Pediatr Pulmonol*. 2006;41:1125-1128.
11. Mielck A, Reitmeir P, Wjst M. Severity of childhood asthma by socioeconomic status. *Int J Epidemiol*. 1996;25:388-393.
12. Cohen S, Berkman N, Picard E, et al. Co-morbidities and cognitive status in a cohort of teenagers with asthma. *Pediatr Pulmonol*. 2016; 51:901-907.
13. American Thoracic Society. Guidelines for methacholine and exercise challenge testing: 1999. *Am J Respir Crit Care Med*. 2000;161: 309-329.
14. Gal R -The selection, classification and placement process Greenwood Press. In: A Portrait of the Israel Soldier. Greenwood Press; 1986:77-96.
15. Ross KR, Hart MA. Assessing the relationship between obesity and asthma in adolescent patients: a review. *Adolesc Health Med Ther*. 2013;4:39-49.
16. Hakala K, Stenius-Aarniala B, Sovijärvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest*. 2000;118: 1315-1321.
17. Maniscalco M, Zedda A, Faraone S, et al. Weight loss and asthma control in severely obese asthmatic females. *Respir Med*. 2008;102: 102-108.
18. Stenius-Aarniala B, Poussa T, Kvarnström J, Grönlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ*. 2000; 320:827-832.
19. Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med*. 2012;106:651-660.
20. Dhabuwala A, Cannan RJ, Stubbs RS. Improvement in co-morbidities following weight loss from gastric bypass surgery. *Obes Surg*. 2000; 10:428-435.
21. Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. *Chest*. 2004;125: 2046-2052.

22. da Silva PL, de Mello MT, Cheik NC, et al. Interdisciplinary therapy improves biomarkers profile and lung function in asthmatic obese adolescents. *Pediatr Pulmonol*. 2012;47:8-17.
23. Negri E, Pagano R, Decarli A, La Vecchia C. Body weight and the prevalence of chronic diseases. *J Epidemiol Community Health*. 1988; 42:24-29.
24. Furukawa T, Hasegawa T, Suzuki K, et al. Influence of underweight on asthma control. *Allergol Int*. 2012;61:489-496.
25. Lang JE, Hossain J, Smith K, Lima JJ. Asthma severity, exacerbation risk, and controller treatment burden in underweight and obese children. *J Asthma*. 2012;49:456-463.
26. Wilson KF1, Spector ME, Orlandi RR. Types of rhinitis. *Otolaryngol Clin North Am*. 2011;44:549-559.
27. Corren J, Barrody FM, Tobias A. Allergic and nonallergic rhinitis. In: Burks W, Holgate ST, O'Hehir RE, Broide DH, Bacharier LB, Khurana Hershey GK, Peebles RS, Jr. *Middleton's Allergy: Principles and Practice*. Electronic edition. Elsevier; 2019;636-658.
28. Bachert C, Van Cauwenberge P, Olbrecht J, Van, Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. *Allergy*. 2006;61:693-698.
29. Aberg N. Birth season variation in asthma and allergic rhinitis. *Clin Exp Allergy*. 1989;19:643-648.
30. Cockcroft D, Beth, Davis B. Direct and indirect challenges in the clinical assessment of asthma. *Ann Allergy Asthma Immunol*. 2009; 103:363-369.

How to cite this article: Goldberg S, Picard E, Joseph L, et al. Factors associated with resolution of childhood asthma by the age of 17: large cohort analysis. *Pediatric Pulmonology*. 2022; 57:878-884. doi:10.1002/ppul.25828