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Prediction of Atopic Asthma in Children with Asthma in Early Life

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ABSTRACT
Background: Childhood asthma is the most frequent chronic non-communicable condition. Preschool and early childhood wheeze is common for many children. Asthma can be a lifelong problem for some children. Atopic asthma is the commonest based on gene–environment interactions identified by international research over the past 20 years.
Objective: This study aimed to predict atopic bronchial asthma in children at risk.
Methods: The present cross-sectional study was carried out on 50 asthmatic patients (29 males and 21 females). Apparently normal 20 children of comparable age, sex and socioeconomic status were taken as a control group. The patients were recruited from Otorhinolaryngology Clinics. They were suspected of atopic asthma with allergic rhinitis or repeated attacks of common cold or other risk factors. The study was conducted through the period from May 2021 to December 2021. **Results:** Asthma was more prevalent in males in 2 groups with significant difference. There were significant differences between asthmatic groups regarding family history of atopic diseases, seasonal variations, serum IgE titer but non-significant regarding parasitic infestations, chest X-ray abnormalities and studied variables. There was significant positive correlation between serum IgE titer and attacks severity, history of atopy and eosinophilia but not with seasonal and diurnal variation. **Conclusion:** The presence of atopic diseases, family history of atopic diseases, high serum eosinophilic count and high serum IgE titer in children with asthma in early life was found to be predictive to the development of persistent asthma in adulthood.
Keywords: Asthma, Atopic, Children, Early Life.

INTRODUCTION

Preschool and early childhood wheeze is a common occurrence for many children. The majority of children grow out of their asthma symptoms, but for some, it might be a lifelong problem. Families and physicians are looking for ways to anticipate the course of sickness in early children [(1)]. There is a growing understanding that the long-term answer to the asthma epidemic rests in prevention rather than in the development of increasingly more sophisticated anti-inflammatory drugs for treatment of established disease [(2)].

The most frequent kind of asthma, atopic asthma, is based on gene–environment interactions that have been identified by international research over the past 20 years. Because current treatment techniques for children with asthma do not affect their long-term prognosis despite reducing symptoms and enhancing quality of life, a new strategy is required [(3)]. The ideal grail of primary prevention is still an unattainable objective because of interactions that are still unknown. However, the progress that has been achieved in this area is sufficient to justify a more structured approach to early identification of high-risk children [(4)].

Childhood asthma is the most frequent chronic non-communicable condition. Recurrent wheezing is common in children, with estimates ranging up to 20%. Some children's wheeze subsides as they become older, while others develop lifelong asthma [(5)]. Types include transient infantile wheeze, in which children have frequent episodes of wheezing for the first two to three years of life but rarely do so afterward, viral-associated wheezing, in which children typically have episodes of wheezing linked to respiratory viral infections but may not wheeze at other times [(6)], and atopic asthma, characterized by wheezing in children who have become hypersensitive to aeroallergens with symptoms of atopy, such as dermatitis and rhino-conjunctivitis [(7)].

Asthma that lasts throughout childhood and into adulthood is the biggest burden on families and the society, and hence is the primary goal of preventative program [(8)]. While the word "persistent asthma" is often associated with the clinical stage of asthma, it is used here to refer to a condition that lasts from infancy into adulthood. Childhood asthma and sensitization to aeroallergens extend into adolescence,4–11 at least in the developed world, and in some circumstances even into early adulthood in certain situations [(9)].

The present study aim was prediction of atopic bronchial asthma in susceptible children in early life.

MATERIAL AND METHODS

The present cross-sectional study was carried out on 50 patients with bronchial asthma disease, 29 males and 21 females with an age range 2-14 years. Apparently normal 20 children of comparable age, sex and socioeconomic status were taken as a control group. The patients were recruited from Otorhinolaryngology Clinics. They were suspected for atopic asthma with allergic rhinitis or repeated attacks of common cold or other risk factors as family history and other atopic diseases affection among the period from May 2021 to December 2021.

Inclusion criteria: The children who have recurrent wheeze during early six years of life. The ability to perform the required spirometry maneuvers in an acceptable and reliable technique.

Exclusion criteria: Children who had any clinical and/or laboratory evidence suggestive of other chest diseases and manifestations of heart failure clinically or subclinically. Children with eosinophilia due to any

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parasitic infestations. Patients aged below six years were excluded from pulmonary function test.

Children have been divided into two groups: Group I Included fifty children with bronchial asthma (29 males and 21 females) and they were subdivided into: Group A consisted of children with suspected early onset bronchial asthma aged from 2-6 years of age (14 males and 11 females) with mean age of 2.94 ± 1.19 years. Group B included children with established bronchial asthma aged from 6-14 years of age (15 males and 10 females) with mean age of 9.73 ± 2.39 years. Group II (control group) included twenty apparently normal children of comparable age, sex and socioeconomic status 9 males and 11 females aged from 2-14 years (10 below 6 years and 10 above 6 years).

All cases were subjected to the following: full history, clinical examination and investigations as absolute eosinophilic count, total IgE titer, complete blood picture, stool analysis, plain X-ray for chest and heart and pulmonary function test (for patients above 6 years).

Ethical considerations:

The study was approved by the Faculty's Ethics Committee of Shebin El-Kom teaching hospital. All the patients were informed about details of the study. Informed written consents were taken from all patients. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Analyses were carried out utilizing IBM-SPSS version 24. (May 2016). It was determined that Kristal-Wallis and Wilcoxon's tests, as well as Spearman's correlations and logistic regression analyses, had statistical significance. Each variable was analyzed in accordance with the type of data it contained (parametric or not). If the P-values ≤ 0.05 we considered the results to be significant.

RESULTS

Table (1) showed that asthma was more prevalent in males in both groups with significant difference. There was significant difference between asthmatic groups as regards family history of atopic disease but no significant difference as regards consanguinity. The table showed that there was significant difference between asthmatic groups as regards atopic diseases and seasonal variations but no significant difference as regards studied variables.

Table (1): Patients basal characteristics

	Groups		**P-value**
	Group A (No %)	Group B (No %)	
Gender **Male** **Female**	 14 (56.0) 11 (44.0)	 15 (60.0) 10 (40.0)	< 0.05 S
Consanguinity Positive Negative	6 (24.0) 19 (76.0)	4 (16.0) 21 (84.0)	>0.05 NS
Family history of atopic disease Positive Negative	13 (52.0) 12 (48.0)	14 (56.0) 11 (24.0)	< 0.05 S
Atopic disease: **No atopy** **Eczema** **Conjunctivitis** **Rhinitis**	 12 (48.0) 3 (12.0) 1 (4.0) 9 (36.0)	 9 (36.0) 2 (8.0) 0 (0.0) 14 (56.0)	< 0.05 S
Severity of attacks: Mild **Moderate** **Severe**	12 (48.0) 9 (36.0) 4 (16.0)	12 (48.0) 7 (28.0) 6 (24.0)	> 0.05 NS
Seasonal variations: **No seasonal variation Winter** **Summer** **Spring**	5 (20.0) 14 (56.0) 4 (16.0) 2 (8.0)	4 (16.0) 11 (44.0) 3 (12.0) 7 (28.0)	< 0.05 S
Diurnal variations: **No diurnal variation** **Night** **Morning**	 7 (28.0) 13 (52.0) 5 (20.0)	 9 (36.0) 9 (36.0) 7 (28.0)	 > 0.05 NS
Precipitating factors of attacks: **No precipitating factors** **Infections** **Odors and food**	 5 (20.0) 18 (72.0) 2 (8.0)	 3 (12.0) 17 (68.0) 5 (20.0)	 > 0.05 NS
Total	25 (100.0)	25 (100.0)	

There was significant difference between asthmatic group (A) and controls as regards BMI but there was no significant difference in group (B) as shown in table (2).

Table (2): Patients' BMI

Studied variables	Studied groups	Number	Mean ± SD	P-value
Body mass index (BMI)	Group A Control group	25 10	12.06 ± 1.62 10.35 ± 1.2	< 0.05 S
	Group B Control group	25 10	18.67 ± 5.96 16.48 ± 2.51	>0.05 NS

There was significant difference between studied groups as regards hemoglobin and leucocytic and eosinophilic counts.

Table (3): Laboratory results of included subjects.

Studied variables	Number	Mean ± SD	p – value	Tamhane Post Hoc p-value
Hemoglobin gm/dl:			< 0.05	
- Group A	25	11.2 ± 1.42	S	P1= > 0.05
- Group B	25	10.1 ± 1.6		P2= < 0.05*
- Control group	20	12.1 ± 3.4		P3= < 0.05*
Leucocytic count c/mm³:			< 0.05	
-Group A	25	11.9 ± 2.3	S	P1= < 0.05*
- Group B	25	12.2±3.1		P2= > 0.05
- Control group	20	3.14±3.01		P3= < 0.05*
Esinophilic count%:				
- Group A	25	5.01±1.11	< 0.05	P1= < 0.05*
- Group B	25	9.88±2.09	S	P2= < 0.05*
- Control group	20	3.1 ± 0.97		P3= < 0.05*

P1: between asthmatic group A and asthmatic group B | P2: between asthmatic group A and control group | P3: between asthmatic group B and control group.

There was significant difference between studied groups as regards eosinophilic count (Table 4).

Table (4): Eosinophilic count in the blood

Eosinophils	Group A No %	Group B No %	Controls No %	P-value
Positive >5% Negative<5%	10 40.0 15 60.0	17 68.0 8 32.0	0 0.0 20 100.0	< 0.05 S
Total	25 100.0	25 100.0	20 100.0	

There was non-significant difference between studied groups as regards parasitic infestations in stool. Table (5) showed that there was significant difference between studied groups as regards the history of atopic diseases.

Table (5): History of atopic diseases

	Group A No %	Group B No %	Controls No %	P-value
Parasitic infestations in stool				
Positive **Negative**	3 12.0 22 88.0	2 6.0 23 94.0	5 25 15 75	> 0.05 NS
Atopic Diseases				
No atopy **Eczema** **Conjunctivitis** **Rhinitis**	12 48.0 3 12.0 1 4.0 9 36.0	9 36.0 2 8.0 0 0.0 14 56.0	14 80.0 1 5.0 0 0.0 3 15.0	< 0.05 S
Total	25 100.0	25 100.0	20 100.0	

There was significant difference between studied groups regarding serum IgE titer (Table 6).

Table (6): Serum IgE titer

Studied variables	Number	Mean ± SD	P-value	Tamhane Post Hoc p-value
IgE titer IU/ml:				
- Group A	25	106.02±13.35	< 0.05	P1= > 0.05
- Group B	25	302.7 ± 27.98	S	P2= < 0.05*
- Control group	20	44.2 ± 4.3		P3= < 0.05*

P1: between asthmatic group A and asthmatic group B | P2: between asthmatic group A and control group | P3: between asthmatic group B and control group.

There was significant positive correlation between serum IgE titer and severity of attacks, history of atopy and eosinophilia but no significant correlation with seasonal and diurnal variation (Table 7).

Table (7): Association between serum IgE titer and subjects variables

Studied variables	IgE titer		P-value
	High titer No %	Within Normal No %	
Severity of attacks: Mild	3 (21.4)	9 (81.8)	
Moderate	7 (50.0)	2 (18.2)	< 0.05
Severe	4 (28.6)	0 (0.0)	S
Seasonal variation: No seasonal			> 0.05
variation Winter	0 (0.0)	5 (45.5)	NS
Summer	9 (64.3)	5 (45.5)	
Spring	4 (28.6)	0 (0.0)	
	1 (7.1)	1 (9.0)	
Diurnal variation:	1 (7.1)	6 (54.5)	
No diurnal variation Night	8 (57.1)	5 (45.5)	< 0.05
Morning	5 (35.8)	0 (0.0)	NS
History of atopy:			
No history of atopy Eczema	4 (28.6)	8 (72.7)	< 0.05
Conjunctivitis	2 (14.3)	1 (9.1)	S
Rhinitis	1 (7.1)	0 (0.0)	
	7 (50.0)	2 (18.2)	
Esinophilia:			< 0.05
Positive	9 (64.3)	4 (36.4)	S
Negative	5 (35.7)	7 (63.6)	

There was no significant difference between studied groups concerning chest X-ray abnormalities (Table 8).

Table (8): Chest X-ray abnormalities in studies groups

Chest X ray	Group A No %	Group B No %	Controls No %	P-value
Bronchovascular marking	3 (12.0)	9 (36.0)	0 (0.0)	
Hyperinflation	2 (8.0)	4 (16.0)	0 (0.0)	> 0.05
Normal	20 (80.0)	12 (48.0)	20 (100.0)	NS
Total	25 100.0	25 100.0	20 100.0	

Pulmonary function test of asthmatic group of 6 years showed children with normal pulmonary function test 5 (20%), with mild obstruction 11 (44%), moderate obstruction 6 (24%) and severe obstruction 3 (12%) as shown in table (9).

Table (9): pulmonary function test of asthmatic group

Variables	Normal	Mild obstruction	Moderate obstruction	Severe obstruction
Mean FVC%	97.87	93.75	90.10	86.35
MeanFEV1%	96.77	84.34	75.65	64.32
FEV1/FVC%	89.12	76.85	68.39	57.56
Mean PEF %	75.97	70.13	64.96	59.60
Total	5	11	6	3
%	20	44	24	12

DISCUSSION

In our study, regarding anthropometric measurements we found that in group (A) the BMI was 12.06 ± 1.62, which was statistical significant compared to control. From the history most of them were obese or may be due to use of corticosteroids as line of treatment in our patients. In group (B), they had higher mean BMI (18.76 ± 5.96), but was not statistically significant compared to control. This is in agreement with **Bonato & Matteo** [10] who demonstrated that the prevalence of obesity among children with asthma is exceedingly high, and it is likely to increase the chance of developing asthma in the first place. On the other hand, **Turturice & Benjamin** [11] demonstrated that the prevalence of obesity in asthmatic kids was neither a risk factor for asthma nor a role in its severity, and that the prevalence of obesity in the control population was not significantly different and that obesity and atopy have no connection.

As regards clinical picture of asthma in asthmatic groups, in group (A) 36% had allergic rhinitis, 12% had eczema and 4% had allergic conjunctivitis and in group (B) 56% had rhinitis, 8% had eczema. By comparing with control group this difference was statistically significant. Also, the most common allergic association in both asthmatic groups was allergic rhinitis. **Ravn & Nina** [12] found that atopic dermatitis constitutes a risk for asthma, but only when associated with allergic sensitization. But, **Korhonen & Päivi** [13] found that atopic dermatitis does not constitute a risk for asthma, but only when associated with allergic sensitization.

In regard to precipitating factors of asthma, there were 72% in group (A) and 68% in group (B) were due to viral infections. About 8% in group (A) and 20% in group (B) were due to odors and food allergy. As previously reported by **Mikhail *et al.*** [14] severe asthma attacks in children older than 2 years of age are frequently accompanied by respiratory viral infections. This finding is in line with our study. But there was disagreement with **Ozdemir *et al.*** [15].

As regards laboratory data, the present study showed that 40% from patients in group (A) and 68% in group (B) had high serum absolute eosinophilic count (>5%). Allergic inflammation is associated with marked infiltration of eosinophils in affected tissues. This is in agreement with the work of **Shareef *et al.*** [16] where eosinophils were found to be essential elements of inflammation in asthmatic airways, and that permanent airway reactivity may result from inflammation and eosinophilic activation. In contrast, **Kuruvilla *et al.*** [17] found that individuals can have severe and chronic asthma without eosinophilic inflammation, as well as an aggravation of asthma without a rise in eosinophilic inflammation.

Our study showed that both asthmatic groups had high total leucocytic count than control group and this was significant difference. The mean in group (B) (12.200c/mm³ ± 3.61) was higher than in group (A) (9.000c/mm³ ± 2.3). Individual inflammatory pathways' involvement to the host's response to respiratory discussion 90 viruses (e.g., respiratory syncytial virus) is unclear, as demonstrated by **Li *et al.*** [18]**. Chen *et al.*** [19] found that, neutrophil inflammation did not explain current asthma or asthma activity.

Concerning parasitic infestations in stool, there were 3 patients in group (A) and 2 patients in group (B) had parasitic infestation like Entropies vermicularis and Ascaris lumbericoides (they had normal serum eosinophilic count). This agrees with **Xing *et el.*** [20] who found that children with high load infestation were five times more likely to have bronchial hyperresponsivness than children with low load or no infestation.

In regard to serum immunoglobulin E titer, our study found that both asthmatic groups had high IgE titer and was higher in group (B) (302.7 IU) than in group (A) (106.02 IU), which was statistically significant. This is in agreement with **Joubert *et al.*** [21] who found that evidence suggests that quantitative measures of atopy, especially cumulative titres of IgE specific for perennial inhalant allergens, provide more assessments of atopy-associated risk.

In our study we found that, there was significant positive correlation between serum IgE titer and severity of attacks, history of atopic diseases and serum eosinophilic count in asthmatic groups as follows: In group (A) 14 patients who had high IgE level showed that 50% had moderate asthmatic attacks, (64.3% in winter and 57.1% at night), 50% had rhinitis and 64.3% had eosinophilia. In group (B) 16 patients who had high IgE level showed that: 37.5% had moderate and 37.5% had severe attacks (50% in winter, 35.7% at night and 35.7% at morning), 64% had rhinitis and 62.5% had eosinophilia. This agrees with **Hameed *et al.*** [22] who found that serum IgE level is a good predictor of allergy in children. It is influenced by exposure to passive smoking, cold, pollens and pets and is associated with serum eosinophilia.

As regards chest X-ray in our study, there were increased bronchovascular markings and hyperinflated chest in group (B) in 36% and 16% respectively and 12% and 8% in group (A). This difference had no statistical significance. So, chest X-ray are often needed to exclude other possible diagnosis or complications as lung atelectasis or pneumonia. It is possible to measure airflow restriction using pulmonary function testing. Spirometry is the gold standard for diagnosing asthma in patients. We only performed pulmonary function testing on asthmatic patients (B) in our study since spirometic tests have proven problematic. Validity and repeatability have been deemed substantially reduced as in **Sirazitdinov *et al.*** [23].

Regarding pulmonary function tests in our study, 20% showed normal tests, 44% showed mild obstruction, 24% showed moderate obstruction and 12% showed severe obstruction. The mean values for forced vital capacity (FVC), forced expired volume in 1 sec

(FEV1) and FEV1/FVC ratio were respectively 97.87%, 96.77% and 89.12%.

This is in agreement with, **Proboszcz *et al*. [24]** who reported that FVC, FEV1 FEV1/FVC ratio and forced expiratory flow (FEF) were 92.7, 92.2, 85.3 and 78.0 percent predicted, respectively. 77% of FEV1 values were ≥ 80%, 18.6% were between 60-80% and 3.1% were <60%.

Similarly **Sason *et al.*** [25] found that 57.45% of children showed normal pulmonary function tests, 30.38% showed mild obstruction, 19.5% showed moderate obstruction and 1.6% showed severe obstruction.

CONCLUSIONS

The presence of atopic diseases, family history of atopic diseases, high serum eosinophilic count and high serum IgE titer in children with asthma in early life was found to be predictive to the development of persistent asthma in adulthood.

Declarations:

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REFERENCES

1. **Douros K, Everard M (2020):** Time to say goodbye to bronchiolitis, viral wheeze, reactive airways disease, wheeze bronchitis and all that. Frontiers in Pediatrics, 8: 218.
2. **Lott C, Truhlář A, Alfonzo A *et al*. (2021):** European Resuscitation Council Guidelines 2021: cardiac arrest in special circumstances. Resuscitation, 161: 152-219.
3. **Hernandez-Pacheco N, Kere M, Melén E (2022):** Gene-environment interactions in childhood asthma revisited; expanding the interaction concept. Pediatric Allergy and Immunology, 33 (5): e13780.
4. **Oliveira L, Gasser T, Edwards R *et al*. (2021):** Alpha-synuclein research: defining strategic moves in the battle against Parkinson's disease. npj Parkinson's Disease, 7 (1): 1-23.
5. **Driscoll A, Arshad S, Bont L *et al*. (2020):** Does respiratory syncytial virus lower respiratory illness in early life cause recurrent wheeze of early childhood and asthma? Critical review of the evidence and guidance for future studies from a World Health Organization-sponsored meeting. Vaccine, 38 (11): 2435-48.
6. **Al-Shamrani A, Bagais K, Alenazi A *et al*. (2019):** Wheezing in children: Approaches to diagnosis and management. International Journal of Pediatrics & Adolescent Medicine, 6 (2): 68.
7. **Agnew M, Banic I, Lake I *et al*. (2018):** Modifiable risk factors for common ragweed (Ambrosia artemisiifolia) allergy and disease in children: a case-control study. International journal of environmental research and public health, 15 (7): 1339.
8. **Lenney W, Bush A, Fitzgerald D *et al.* (2018):** Improving the global diagnosis and management of asthma in children. Thorax, 73 (7): 662-9.
9. **Dharmage S, Perret J, Custovic A (2019):** Epidemiology of asthma in children and adults. Frontiers in pediatrics, 7: 246.
10. **Bonato M, Bazzan E, Snijders D *et al*. (2018):** Clinical and pathologic factors predicting future asthma in wheezing children. A longitudinal study. American journal of respiratory cell and molecular biology, 59 (4): 458-66.
11. **Turturice B, Gold D, Litonjua A *et al*. (2019):** Lower perinatal exposure to Proteobacteria is an independent predictor of early childhood wheezing. Journal of Allergy and Clinical Immunology, 143 (1): 419-21. e5.
12. **Ravn N, Halling A, Berkowitz A *et al*. (2020):** How does parental history of atopic disease predict the risk of atopic dermatitis in a child? A systematic review and meta-analysis. Journal of Allergy and Clinical Immunology, 145 (4): 1182-93.
13. **Korhonen P, Haataja P, Ojala R *et al*. (2018):** Asthma and atopic dermatitis after early-, late-, and post-term birth. Pediatric pulmonology, 53 (3): 269-77.
14. **Mikhail I, Grayson M (2019):** Asthma and viral infections: An intricate relationship. Annals of Allergy, Asthma & Immunology, 123 (4): 352-8.
15. **Ozdemir P, Celik V (2022):** Current Recommendations on the Management of Pediatric Asthma and Allergic Rhinitis during the COVID-19 Pandemic versus Real-Life Practice. International Archives of Allergy and Immunology, 183 (2): 217-24.
16. **Shareef S, Amin K, Janson C (2021):** The Association Between β-Dystroglycan in Airway Smooth Muscle and Eosinophils in Allergic Asthma. Inflammation, 44 (3): 1060-8.
17. **Kuruvilla M, Lee F, Lee G (2019):** Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clinical reviews in allergy & immunology, 56 (2): 219-33.
18. **Li H, Lin Y, Ye Q *et al.* (2020):** Airway inflammation and remodeling of cigarette smoking exposure ovalbumin-induced asthma is alleviated by CpG oligodeoxynucleotides via affecting dendritic cell-mediated Th17 polarization. International Immunopharmacology, 82: 106361.
19. **Chen S, Deng Y, He Q *et al.* (2020):** Toll-like receptor 4 deficiency aggravates airway hyperresponsiveness and inflammation by impairing neutrophil apoptosis in a toluene diisocyanate-induced murine asthma model. Allergy, Asthma & Immunology Research, 12 (4): 608.
20. **Xing Y, Wang M, Leung T *et al*. (2022):** Poultry exposure and environmental protection against asthma in rural children. Allergy, 9(5):1-12.
21. **Joubert A, Geppert M, Johnson L *et al*. (2020):** Mechanisms of particles in sensitization, effector function and therapy of allergic disease. Frontiers in Immunology, 11: 1-20.
22. **Hameed R, Ahmed M, Abood H *et al*. (2019):** To evaluate total serum immunoglobulin E level and factors that effect on this level in Iraqi asthmatic children. Biomedical and Biotechnology Research Journal (BBRJ), 3 (4): 240.
23. **Sirazitdinov I, Kholiavchenko M, Mustafaev T *et al*. (2019):** Deep neural network ensemble for pneumonia localization from a large-scale chest x-ray database. Computers & electrical engineering, 78: 388-99.
24. **Proboszcz M, Mycroft K, Paplinska-Goryca M *et al*. (2019):** Relationship between blood and induced sputum eosinophils, bronchial hyperresponsiveness and reversibility of airway obstruction in mild-to-moderate chronic obstructive pulmonary disease. COPD: Journal of Chronic Obstructive Pulmonary Disease, 16 (5-6): 354-61.
25. **Sason Y, Oksenberg A, Sobel J *et al.* (2022):** Characteristics of patients with positional OSA according to ethnicity and the identification of novel phenotype-Lateral Positional Patients (Lateral PP): A MESA study. Characteristics of patients with positional OSA according to ethnicity and the identification of a novel phenotype – Lateral Positional Patients (Lateral PP): A MESA study | medRxiv