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### RESEARCH ARTICLE

#### EMOTIONAL AND PROSOCIAL BEHAVIOURAL PROBLEMS AMONG SAUDI CHILDREN WITH ATOPIC DERMATITIS

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#### Abstract

**Background:** Atopic dermatitis (AD) is one of the most prevalent chronic conditions in children. It is a global public health concern because of its burden on the health systems. The disease is usually associated with comorbidities including psychosocial and behavioural problems.

**Objectives:** To explore the emotional symptoms and peer relationship problems, hyperactivity/inattention, and prosocial behaviour among Saudi children with atopic dermatitis

**Methods:** A cross-sectional study was conducted during November 2022 through an online survey using the short form of the Strengths and Difficulties Questionnaire. Parents of Saudi children from all over Saudi Arabia were recruited. Non-Saudi participants, subjects who refused to participate, and those with incomplete data were excluded.

**Results:** During the past 12 months, 44.1% of children had eczema/skin allergy. Overall, 44.0% of atopic children had an abnormal Strengths and Difficulties Questionnaire categorization. The emotional problems subscale represent 36.0% while the prosocial subscales was 24.0%. Mental impairment was significantly associated with higher number of children in the family ( $p = 0.019$ ), parental smoking ( $p = 0.038$ ), as well as history of asthma ( $p = 0.004$ ), deficit-hyperactivity disorder ( $p < 0.001$ ), and autism ( $p = 0.002$ ).

**Conclusion:** Our study supports the existing literature on the presence of associations between AD and mental health disorders in children. High number of children in the family, parent smoking, history of asthma, attention deficit-hyperactivity disorder, and autism were predictors of mental health impairment. There is a need to screen patients for mental health impairment to ensure better outcome.

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#### Introduction:-

Atopic dermatitis is a chronic inflammatory skin condition. It is also known as eczema or atopic eczema, and it is the most common inflammatory skin disease. Worldwide, AD has been estimated to affect up to 15% to 20% of paediatric populations and up to 10% of adult populations (1, 2). In Saudi Arabia, AD is found to be the most prevalent chronic condition in children, and it affects more than one thirds of Saudi children (3). The disease

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represents a critical global public health concern because of its increasing prevalence and the subsequent rising financial burden on health systems (4, 5, and 6)

Added to various associated comorbidities, patients with AD experience insistent pruritus, which is the primary manifestation of the disease. The manifestations of the disorder are usually associated with significant negative impacts on the child's quality of life as well as his family(7). Recent research has highlighted several important systemic comorbidities. Increasing evidence supports the presence of strong associations between ad and anxiety, depression, and suicidality (8, 9, 10)

Children with AD have not only psychosocial and behavioural issues, such as irritability, crying, and fearfulness but also several physical manifestations (e.g., asthma, food allergy, allergic rhinitis, and cutaneous infections) (11,12,13,14). Recently, more well-defined mental health disorders including attention-deficit/hyperactivity disorder, anxiety, depression, conduct disorder, and autism have been linked to AD (15,16)

Paediatric depression often presents with subtle symptoms and is underdiagnosed and undertreated. Internalizing behaviours (e.g., behaviours directed inward that are indicative of a child's emotional and psychological states) include depressive behaviour, anxious behaviour, and somatic complaints, and they can be used to identify children who may require early intervention (17, 18, 19)

A variety of possible mechanisms have been investigated to explain the potential association between AD and mental health disorders. These include associations with other atopic diseases (such as bronchial asthma), disturbed sleep (20), supposed social stigma, and lifestyle changes, such as exercise restriction due to sweat-induced itching. Multiple studies have also found that some subtypes of depression are associated with increased markers of systemic inflammation such as IL-6 and CRP (21, 22). These biomarkers may be elevated in patients with AD (23, 24).

The impact of childhood AD on mental health is not well understood (25). Although earlier studies have reported greater prospects of mental health impairment among children with AD, this has not been investigated in Saudi Arabia. In addition, most of these studies need further confirmation due to several inherent limitations including the small sample size.

Therefore, this study aimed to investigate the association between AD and mental health impairment and estimate the prevalence of AD and mental impairment among Saudi children.

## **Methods:-**

### **Study design, setting, and data**

This cross-sectional survey study was conducted during November 2022. We enrolled parents of Saudi children from all over Saudi Arabia. Non-Saudi participants, subjects who refuse to participate, and those with incomplete data were excluded.

### **Study tool and its validation**

Data were collected by an online, self-administered questionnaire. An electronic survey was created using Google Forms for data collection. The questionnaire was disseminated using different social media platforms, such as Facebook, Twitter, Instagram, and WhatsApp. The outcome measures included a) prevalence of AD among Saudi children; b) prevalence of mental impairment among Saudi children with AD; and c) predictors of mental impairment among Saudi children with AD. The survey collected data including sociodemographic as well as health and functional status of the participants' children using the short form of the Strengths and Difficulties Questionnaire (26). It included 25 items comprising 5 scales of 5 items each. The scales were about the followings: 1) emotional symptoms, 2) conduct problems, 3) hyperactivity/inattention, 4) peer relationships problem, and 5) prosocial behaviour.

### **Sampling and sample size**

A cluster random sampling technique was used to select participants depending on the distribution of Saudi people in percentage according to the 2017 estimates (20) was estimated to be 29% from Western region (123 participants), 28% from Central region (119 participants), 20% from Northern region (42 participants), 19% from Southern region (79 participants), and 15% from Eastern Province (64 participants). The sample size was estimated with an online sample size calculator (Raosoft, <http://www.raosoft.com/samplesize.html>) using a margin of error of 5% and a

confidence interval of 95%, assuming an average response for most of the questions of 50%, and depending on an average Saudi children population size of 8,556,493(27). The required sample size is 385 participants. It was increased to 424 by 39, in a percentage of 10%, to compensate for possible drop out or incomplete response.

**Statistical analysis**

The statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS Statistics) version, version 26 for Windows (IBM Corp., Armonk, N.Y., USA). Categorical variables (e.g., age groups, sex) were expressed as counts and percentages. Numerical variables (i.e., score results) were summarized as the mean, standard deviation, median and range. The association of the categories of the total score of the Strengths and Difficulties Questionnaire with the parents' and children's characteristics was assessed using Pearson's Chi-square and Fisher-Freeman-Halton exact tests. The statistical significance of the test results was set at a p-value<0.05.

**Results:-**

Out of 520 participants, five parents declined to participate, and the response rate was thus 99%. The characteristics of the participants and their children are summarized in Table 1. The age of the children ranged from 4 to 10 years in 48% of responses and 11 to 17 years in 52%. The distribution of female and male children was nearly equal. Most children resided in urban areas (83.3%). Most parents were employed (87.6%) and more than half of them had a university degree (58.3%). The monthly family income ranged from 5,000 - 10,000 SR in 45.8% of participants. Most families include both parents (87.2%) had three or more children (65.4%). Most parents were non-smokers (61.2%). History of asthma, hay fever, respiratory allergy, ADHD, and autism was reported by 28.7%, 8.5%, 36.1%, 14.0%, and 5.2% of participants respectively. During the past 12 months, 44.1% of children had eczema/skin allergy (Figure 1).

The responses of the parents to the Strengths and Difficulties Questionnaire are presented in Table 2. The most frequent abnormalities were having many fears (22.4%) in the emotional problems subscale; having tantrums/hot temper (25.9%) in the conduct problems subscale; constant fidgeting (29.8%) in the hyperactivity subscale; being bullied (52.7%) in the peer problem subscale; and lack of volunteering to help others (21.0%) in the prosocial subscale. Table 3 shows the summary statistics of the subscales and the total score of the Strengths and Difficulties Questionnaire.

The subscales and the total score of the Strengths and Difficulties Questionnaire were categorized into normal, borderline, and abnormal groups (Table 4). Overall, 44.0% of atopic children had an abnormality while 16.0% were borderline (Figure 2). Regarding the subscales of the questionnaire, abnormalities were detected mostly in the peer problems subscale (46.7%), followed by the conduct problems subscale (46.2%), and then the emotional problems subscale (36.0%). The least abnormalities were observed in the prosocial and hyperactivity subscales (24.0% and 16.4%, respectively; Table 4).

The three categories of the total score of the Strengths and Difficulties Questionnaire were compared regarding the characteristics of the parents and children (Table 5). Mental impairment was significantly associated with having higher number of children in the family (p = 0.019), parental smoking (p = 0.038), as well as having history of asthma (p = 0.004), ADHD (p <0.001), and autism (p = 0.002).

**Discussion:-**

The study evaluated the behavioural problems associated with AD in children using SDQ which is a known screening tool for the behavioural difficulties. As SDQ contains 25 items divided as 5 subscales, the study focused on one difficulty subscale "emotional" and one strength subscale "prosocial".

Atopic dermatitis is one of the most common skin diseases in children. A highly pruritic eczematous lesions on clinical examination are the main diagnostic feature in addition to the genetic, environmental, and neuroimmune factors which interrupt the skin barrier (28, 29, and 30).As AD varies with age, in infants, lesions are usually on the head, trunk, and extensor surfaces of the extremities while in children, the flexor surfaces of the extremities are mainly affected (31).Interestingly, the disease is one of the most prevalent dermatological diseases in Saudi Arabia.This study showed 44.1% of children suffered from eczema in the past 12 months which is comparable to a prevalence observed in a study conducted in King Abdul-Aziz University Hospital (Jeddah) among 1244 dermatology cases(32).Other studies proved similar prevalence in Saudi Arabia(33, 34).

Further, the impact of AD on children's quality of life was comparable to other childhood chronic diseases such as cystic fibrosis (35) and the mental health disorders associated with such disorders is poorly understood. In fact, one of the most important negative personal judgment in dermatology is stigmatization as visible symptoms in the skin appearance may lead to absence of acceptance, increased anxiety, or social avoidance and therefore these are potentially discriminating (36). Disrupted sleep by pruritus associated with inattention and behavioural disorders (37, 38). Our results add to the existing literature indicating that mental health disturbances are common in children with AD (39, 40, 41, and 42). Further study reported a strong association between AD and schizophrenia (43).

The Strengths and Difficulties Questionnaire (SDQ) is a validated behavioural screening tool used for assessment of mental health symptoms (44). Abnormal emotional scale (as measured by a score above 4) was recorded in 36% of the patients. This is in accordance with other studies reporting emotional problems in children with AD (43).

Abnormal score of hyperactivity subscale (above 7) was observed in 16.4% of our studied patients. Several studies reported attention deficit hyperactivity disorder may have a relationship with AD. In fact, low birth weight, parental smoking, and low socioeconomic status are risk factors for both conditions (45, 46, 47, and 48). Further research is needed to examine the relationship between the two disorders. In addition, abnormal peer score (above 4) was observed in 46.7% of patients. That is explained by the effect of AD on poor relationships with other kids and siblings reported by other studies (16, 25).

Little is known about the predictors and trends of psychological comorbidities in paediatric AD. In our study, mental impairment and abnormal SDQ categorization was significantly associated with higher number of children in the family, parental smoking, and history of asthma, ADHD, or autism. Several studies in the literature attempted to identify predictors of psychological disturbances, and they revealed variable results. Atopic comorbidities were mentioned among the predictors of psychological impairment along white race and low family income (42). A study demonstrated that gender, social class, and educational level of the parent as being associated with symptoms of depression in AD patients (43).

According to the growing evidence, there is a need for clinicians to screen for mental health symptoms among AD patients. The screening should include behavioural, functional, and relationship issues and not exclusively depression or anxiety. Additional research is necessary to validate the optimal approach of assessment of the psychological burden of paediatric AD.

The study has several limitations to note. First, the study design was cross-sectional, which precludes any conclusions about the directionality of association between AD and emotional and prosocial problems. Second, AD was assessed using a caregiver's report based on a single question in which this method has 96% specificity, and 70% sensitivity. Third, the short SDQ is a screening tool with high negative predictive value (88-95%) but only modest positive predictive value (51-73%). The false-positive cases of MDI may also partly explain the underutilization of mental health services observed in this study, however they do not account for the gaps entirely.

### **Conclusion:-**

Our study is an attempt to add and highlight the growing evidence that AD is associated with a wide spectrum of mental health disorders. Having higher number of children in the family, parental smoking, and history of asthma, ADHD, or autism had a significant association with mental impairment in our study. Mental health disorders should be considered by clinicians dealing with AD patients.

### **Ethics declarations**

#### **Ethics approval and consent to participate**

Ethical approval for this study was granted by the Ethics Committee of the Ministry of Health Administration at Tabuk city (No.TU-077/022/167). The approval included the research protocol data, collection of informed consent forms from participants, and the final report submitted at the end of the study. Participants were asked to give their consent to participate in the study before starting to fill the questionnaire. They were informed about the study objectives, methodology, risks, and benefits. The Investigators were responsible for keeping the participants' privacy and security of the data. Personal information (e.g., name) were not included in the study data entry software to conserve the participants' privacy. Each subject got a unique identifier code

**Table 1:-** Characteristics of the participants and their children.

Characteristics of the participants and their children		Total n = 515
Age (year)	4 - 10 years	247 (48.0%)
	11 - 17 years	268 (52.0%)
Sex	Female	257 (49.9%)
	Male	258 (50.1%)
Residence	Rural	86 (16.7%)
	Urban	429 (83.3%)
Nationality	Non-Saudi	23 (4.5%)
	Saudi	492 (95.5%)
Employment status of parent	Employed	451 (87.6%)
	Unemployed	64 (12.4%)
Monthly family income (SR)	< 5,000	93 (18.1%)
	5,000 - 10,000	236 (45.8%)
	> 10,000	186 (36.1%)
Level of parental education	Illiterate	12 (2.3%)
	Read and write	24 (4.7%)
	Primary school	9 (1.7%)
	Intermediate school	23 (4.5%)
	Secondary school	77 (15.0%)
	University degree	300 (58.3%)
	Postgraduate degree	70 (13.6%)
Parental presence in the family	Both mother & father	449 (87.2%)
	Father only	288 (5.6%)
	Mother only	48 (9.3%)
Number of children in the family	One	68 (13.2%)
	Two	110 (21.4%)
	Three or more	337 (65.4%)
Parent smoking	No	315 (61.2%)
	Yes	200 (38.8%)
History of asthma	No	367 (71.3%)
	Yes	148 (28.7%)
History of hay fever	No	471 (91.5%)
	Yes	44 (8.5%)
History of respiratory allergy	No	329 (63.9%)
	Yes	186 (36.1%)
History of attention deficit hyperactivity disorder	No	443 (86.0%)
	Yes	72 (14.0%)
History of autism	No	488 (94.8%)
	Yes	27 (5.2%)
During the past 12 months, has the child had eczema or any kind of skin allergy?	No	288 (55.9%)
	Yes	227 (44.1%)

**Table 2:-** Responses to the Strengths and Difficulties Questionnaire by parents of atopic children.

	Not true	Somewhat true	Certainly true
<b>Emotional problems scale</b>			
Q3-Often complains of headaches, stomach-aches, or sickness	113 (50.2%)	70 (31.1%)	42 (18.7%)
Q8-Many worries; often seems worried	111 (49.6%)	71 (31.7%)	42 (18.8%)
Q13-Often unhappy, down-hearted or tearful	98 (43.8%)	86 (38.4%)	40 (17.9%)
Q16-Nervous or clingy in new situations, easily loses confidence	98 (43.6%)	82 (36.4%)	45 (20.0%)
Q24-Many fears, easily scared	72 (32.3%)	101 (45.3%)	50 (22.4%)
<b>Conduct problems scale</b>			
Q5-Often has temper tantrums or hot tempers	80 (35.7%)	86 (38.4%)	58 (25.9%)
Q7-Generally obedient, usually does what adults request	51 (23.1%)	118 (53.4%)	52 (23.5%)

Q12-Often fights with other children or bullies them	121 (54.5%)	73 (32.9%)	28 (12.6%)
Q18-Often lies or cheats	120 (53.6%)	67 (29.9%)	37 (16.5%)
Q22-Steals from home, school or elsewhere	153 (68.6%)	53 (23.8%)	17 (7.6%)
<b>Hyperactivity scale</b>			
Q2-Restless, overactive, cannot stay still for long	82 (36.4%)	100 (44.4%)	43 (19.1%)
Q10-Constantly fidgeting or squirming	82 (36.4%)	76 (33.8%)	67 (29.8%)
Q15-Easily distracted, concentration wanders	90 (40.2%)	80 (35.7%)	54 (24.1%)
Q21-Thinks things out before acting	49 (22.0%)	122 (54.7%)	52 (23.3%)
Q25-Sees tasks through to the end, good attention span	53 (23.7%)	114 (50.9%)	57 (25.4%)
<b>Peer problems scale</b>			
Q6-Rather solitary, tends to play alone	116 (52.0%)	69 (30.9%)	38 (17.0%)
Q11-Has at least one good friend	30 (13.3%)	72 (32.0%)	123 (54.7%)
Q14-Generally liked by other children	20 (8.9%)	95 (42.2%)	110 (48.9%)
Q19-Picked on or bullied by other children	117 (52.7%)	75 (33.8%)	30 (13.5%)
Q23-Gets on better with adults than with other children	72 (32.0%)	102 (45.3%)	51 (22.7%)
<b>Prosocial scale</b>			
Q1-Considerate of other people's feelings	32 (14.2%)	95 (42.2%)	98 (43.6%)
Q4-Shares readily with other children (treats, toys, pencils etc.)	36 (16.1%)	86 (38.4%)	102 (45.5%)
Q17-Kind to younger children	30 (13.5%)	71 (31.8%)	122 (54.7%)
Q20-Often volunteers to help others (parents, teachers, other children)	47 (21.0%)	99 (44.2%)	78 (34.8%)

**Table 3:-** Summary responses the subscales of the Strengths and Difficulties Questionnaire.

	Mean	Standard Deviation	Median	Range (Minimum Maximum)
<b>Emotional problems scale</b>	3.77	2.51	4.00	0.00 - 10.00
<b>Conduct problems scale</b>	3.50	2.21	3.00	0.00 - 10.00
<b>Hyperactivity scale</b>	4.57	2.28	4.00	0.00 - 10.00
<b>Peer problems scale</b>	3.36	1.83	3.00	0.00 - 9.00
<b>Prosocial scale five</b>	6.41	2.73	6.25	0.00 - 10.00
<b>SDQ total score</b>	15.20	6.89	16.00	2.00 - 33.00

**Table 4:-** Categorization of the subscales and the total scale of the strengths and Difficulties Questionnaire.

Scales		N (%)
<b>Emotional</b>	<b>Normal (0 - 3)</b>	108 (48.0%)
	<b>Borderline (4)</b>	36 (16.0%)
	<b>Abnormal (5 - 10)</b>	81 (36.0%)
<b>Conduct</b>	<b>Normal (0 - 2)</b>	82 (36.4%)
	<b>Borderline (3)</b>	39 (17.3%)
	<b>Abnormal (4 - 10)</b>	104 (46.2%)
<b>Hyperactivity</b>	<b>Normal (0 - 5)</b>	154 (68.4%)
	<b>Borderline (6)</b>	34 (15.1%)
	<b>Abnormal (7 - 10)</b>	37 (16.4%)
<b>Peer</b>	<b>Normal (0 - 2)</b>	81 (36.0%)
	<b>Borderline (3)</b>	39 (17.3%)
	<b>Abnormal (4 - 10)</b>	105 (46.7%)
<b>Prosocial</b>	<b>Normal (6 - 10)</b>	137 (60.9%)
	<b>Borderline (5)</b>	34 (15.1%)
	<b>Abnormal (0 - 4)</b>	54 (24.0%)
<b>SDQ</b>	<b>Normal (0 - 13)</b>	90 (40.0%)
	<b>Borderline (14 - 16)</b>	36 (16.0%)
	<b>Abnormal (17 - 40)</b>	99 (44.0%)

**Table 5:-** Comparison of the categories of SDQ score regarding the participants' and children's characteristics.

		SDQ categorization			Statistical tests	
		Normal (0 - 13)	Borderline (14 - 16)	Abnormal (17 - 40)	X <sup>2</sup>	p-value
Age (year)	4 - 10 years	48 (44.0%)	18 (16.5%)	43 (39.4%)	1.891 *	0.288
	11 - 17 years	42 (36.2%)	18 (15.5%)	56 (48.3%)		
Sex	Female	50 (44.6%)	17 (15.2%)	45 (40.2%)	2.036 *	0.361
	Male	40 (35.4%)	19 (16.8%)	54 (47.8%)		
Residence	Rural	13 (36.1%)	4 (11.1%)	19 (52.8%)	1.553 *	0.460
	Urban	77 (40.7%)	32 (16.9%)	80 (42.3%)		
Nationality	Non-Saudi	4 (40.0%)	4 (40.0%)	2 (20.0%)	4.408 **	0.086
	Saudi	86 (40.0%)	32 (14.9%)	97 (45.1%)		
Employment status of parent	Employed	82 (42.1%)	31 (15.9%)	82 (42.1%)	2.843 **	0.253
	Unemployed	8 (26.7%)	5 (16.7%)	17 (56.7%)		
Monthly family income (SR)	< 5,000	13 (32.5%)	8 (20.0%)	19 (47.5%)	4.805 *	0.308
	5,000 - 10,000	39 (36.1%)	19 (17.6%)	50 (46.3%)		
	> 10,000	38 (49.4%)	9 (11.7%)	30 (39.0%)		
Level of parental education	Illiterate	2 (28.6%)	2 (28.6%)	3 (42.9%)	17.098 *	0.146
	Read and write	3 (21.4%)	4 (28.6%)	7 (50.0%)		
	Primary school	2 (40.0%)	0 (0.0%)	3 (60.0%)		
	Intermediate school	3 (25.0%)	0 (0.0%)	9 (75.0%)		
	Secondary school	14 (38.9%)	9 (25.0%)	13 (36.1%)		
	University degree	54 (47.8%)	16 (14.2%)	43 (38.1%)		
	Postgraduate degree	12 (31.6%)	5 (13.2%)	21 (55.3%)		
Parental presence in the family	Both mother and father	79 (41.8%)	26 (13.8%)	84 (44.4%)	5.267 **	0.242
	Father only	3 (23.1%)	4 (30.8%)	6 (46.2%)		
	Mother only	8 (34.8%)	6 (26.1%)	9 (39.1%)		
Number of children in the family	One	13 (54.2%)	6 (25.0%)	5 (20.8%)	11.487 ††	0.019 #

	<b>Two</b>	15 (27.3%)	12 (21.8%)	28 (50.9%)	**	
	<b>Three or more</b>	62 (42.5%)	18 (12.3%)	66 (45.2%)		
<b>Parent smoking</b>	<b>No</b>	54 (46.2%)	21 (17.9%)	42 (35.9%) ‡‡	6.52 3 *	0.038 #
	<b>Yes</b>	36 (33.3%)	15 (13.9%)	57 (52.8%) ††		
<b>History of asthma</b>	<b>No</b>	61 (46.2%)	25 (18.9%)	46 (34.8%) ‡‡	10.8 84 *	0.004 #
	<b>Yes</b>	29 (31.2%)	11 (11.8%)	53 (57.0%) ††		
<b>History of hay fever</b>	<b>No</b>	82 (42.3%)	31 (16.0%)	81 (41.8%)	3.43 3 **	0.176
	<b>Yes</b>	8 (25.8%)	5 (16.1%)	18 (58.1%)		
<b>History of respiratory allergy</b>	<b>No</b>	50 (42.7%)	19 (16.2%)	48 (41.0%)	0.95 5 *	0.620
	<b>Yes</b>	40 (37.0%)	17 (15.7%)	51 (47.2%)		
<b>History of attention deficit hyperactivity disorder</b>	<b>No</b>	86 (47.0%) ††	27 (14.8%)	70 (38.3%) ‡‡	20.3 05 *	<0.00 1#
	<b>Yes</b>	4 (9.5%) \$-	9 (21.4%)	29 (69.0%) ††		
<b>History of autism</b>	<b>No</b>	87 (42.0%)	36 (17.4%)	84 (40.6%) ‡‡	11.9 02 **	0.002 #
	<b>Yes</b>	3 (16.7%)	0 (0.0%)	15 (83.3%) ††		

†: Pearson's Chi-Square test; \*\*: Fisher-Freeman-Halton exact test; # significant at  $p < 0.05$ ; ††: significantly higher than other categories (based on adjusted residuals); ‡‡: significantly lower than the other categories (based on adjusted residuals).



### Prevalence of atopic dermatitis

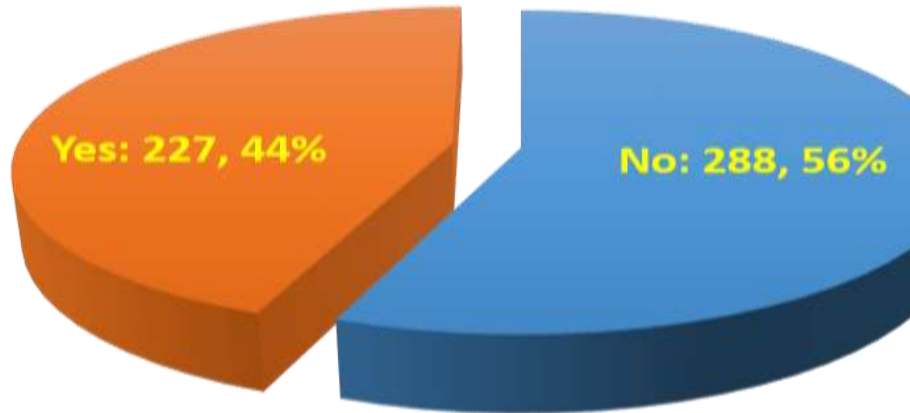


Figure 1. Prevalence of atopic children among the studied sample.

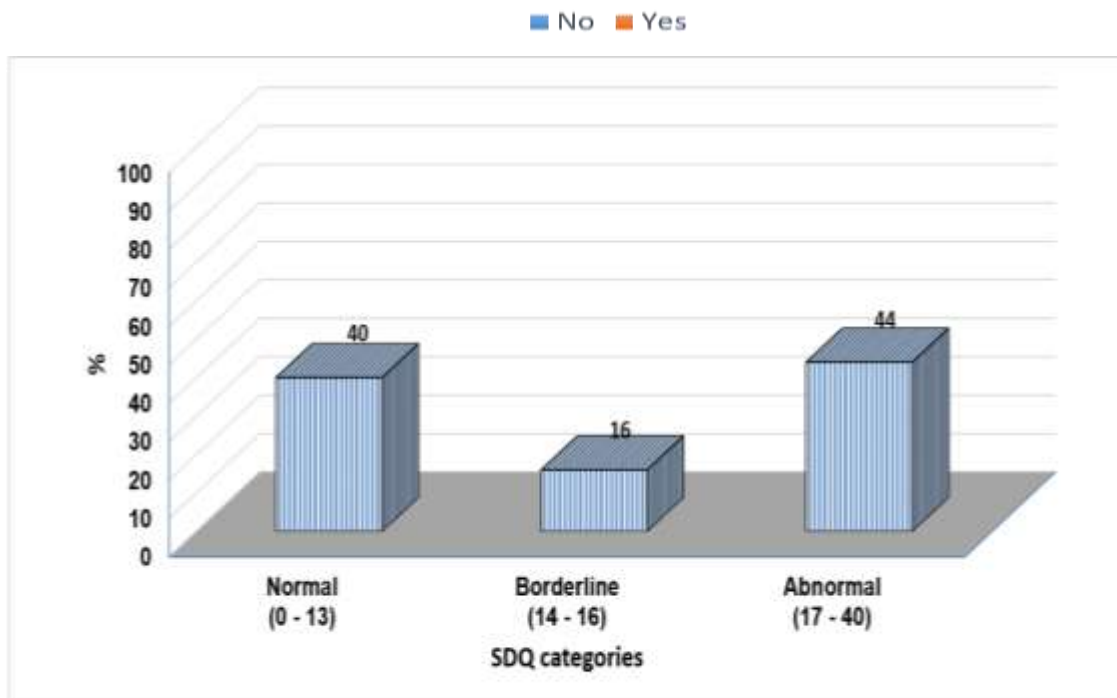


Figure 2. Categories of the total score of the Strengths and Difficulties Questionnaire in atopic children

**Conflict of interest**

The authors stated that they have no conflict of interest

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**Data availability**

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

**Author contribution**

LB, AA, and SW formulated the study design and outlined the data for analysis, wrote the initial and final drafts of the paper, and organized the references.

AH and SE contributed to statistical analysis and results in parts and was responsible for determining the focus, type, and analysis of data, in addition to revising the manuscript.

RE, SO and KJ was involved in detailed data analysis, contributed to the design and presentation of the data, reviewed the contribution of the statistician, and revised the final manuscript.

LB, AF and AQ was involved in writing the main text, including the discussion; revising the contributions to the paper from other authors; reading and approving the final manuscript.

All authors read and approved the final manuscript.

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