Eczema among adolescents in Kuwait: prevalence, severity, sleep disturbance, antihistamine use, and risk factors

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Declaration of competing interests

The authors report no competing interests.

Ethics statement

The study was approved by the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait (no. 2016/451). Written informed consent was obtained from the parents or legal guardians to enroll children in the study.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, AH Ziyab, upon reasonable request.

Author's consent for publication

We give our consent for the publication of this manuscript to be published in the World Allergy Organization Journal, if it is accepted for publication.

Submission declaration

We confirm that this manuscript has not been submitted or is not simultaneously being submitted elsewhere, and that no portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes.

Author Contributions

AHZ conceived, designed, and planned the study, obtained funding, supervised the research conducted, analyzed and interpreted the data, and drafted the manuscript. JWH, YA, HZ, and WK contributed to the study conception, design and planning, contributed to data interpretation, and critically revised the manuscript. All authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by all authors.

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ABSTRACT

Background: Eczema (atopic dermatitis) is a common inflammatory skin disease that is more prevalent in children and adolescents than adults. In Kuwait, there is a lack of empirical knowledge on eczema epidemiology among adolescents. Therefore, this study aimed to estimate the prevalence of eczema symptoms and severity, assess the frequency of eczema-related nocturnal sleep disturbance and its relation to antihistamine use, and determine factors that are associated with eczema prevalence and eczema-related nocturnal sleep disturbance.

Methods: A school-based cross-sectional study enrolled adolescents (n = 3,864) aged 11–14 years across Kuwait. Information on eczema symptoms and clinical history, use of antihistamines, parental history of eczema, mode of delivery, and childhood life-style factors and exposures were reported by parents. Current eczema was defined as chronic or chronically relapsing itchy dermatitis with characteristic morphology and distribution in the past 12 months. Among subjects reporting current itchy rash, frequency of nocturnal sleep disturbance due to itchy rash in the past 12 months was reported as: never, <1 night per week, and ≥1 nights per week. Associations were assessed by applying a modified Poisson regression to estimate adjusted prevalence ratios (aPR) and 95% confidence intervals (CI).

Results: The prevalence estimate of current (past 12 months) itchy rash was 20.5% (735/3,593) and current eczema was 10.2% (388/3,791), with 19.5% (736/3,775) reporting history of ever doctor-diagnosed eczema. Among subjects with current itchy rash, nocturnal sleep disturbance due to itchy rash affected 21.7% (157/724) of participants for <1 night per week and affected 12.7% (92/724) of participants for ≥1 nights per week. Antihistamine use at least once per month increased as the frequency of nocturnal sleep disturbance due to itchy rash increased (P_{trend} <0.001). Factors that demonstrated association with current eczema prevalence included

underweight body mass index (aPR = 1.71, 95% CI: 1.16-2.53), cesarean section delivery (1.29, 1.01-1.65), and maternal (1.72, 1.35-2.19) and paternal (1.83, 1.44-2.32) history of eczema. Frequent (≥1 nights per week) nocturnal sleep disturbance was associated with cesarean section delivery (1.98, 1.37-2.85), exposure to household tobacco smoke (1.70, 1.18-2.47), and dog-keeping (1.93, 1.06-3.52).

Conclusions: Eczema symptoms are common among adolescents in Kuwait, with similar epidemiological patterns as those observed in western countries. A large proportion of affected adolescents reported nocturnal sleep disturbance due to itchy rash. Modifiable risk factors were associated increased prevalence of eczema and night awakenings.

Keywords: eczema, atopic dermatitis, risk factors, sleep, antihistamines.

INTRODUCTION

Eczema (also known as atopic dermatitis or atopic eczema) manifests as a chronically relapsing inflammatory skin disease that follows a waxing-waning course. Although the clinical presentation of the disease is heterogeneous and varies by age and race/ethnicity, common clinical features of eczema include intense itching (pruritus), erythematous patches with edema, dry skin (xerosis), thickening of affected skin, oozing, erosions, and crusting of acute lesions [1, 2]. Eczema is not a life-threatening disease, nonetheless, its manifestations can cause sleep disturbance, low quality of life, and psychosocial disorders [3-5]. In terms of disability-adjusted life years (DALYs), a 2017 global burden of disease (GBD) analysis showed that eczema accounted for 0.36% of the total global DALYs and ranked 59th among all diseases and 15th among nonfatal diseases [6]. Of all skin diseases, eczema had the highest estimated DALYs (123 DALYs per 100,000 subjects), followed by psoriasis (70 DALYs per 100,000 subjects) [6].

Global estimates suggest that eczema affects up to 10% of adults and up to 20% of children and adolescents [7, 8]. Eczema has been viewed as a disease of early childhood as most cases develop during early life [9]. However, recent reports have shown that adult-onset eczema is not rare, with a meta-analysis estimating that approximately 1 in 4 adults with eczema report adulthood-onset [10]. Based on long-term developmental trajectories of eczema analyses, affected individuals, most likely, may follow an early-onset persistent, early/mid-onset resolving, or a late-onset trajectory (disease course) [11-14]. Moreover, it has been shown that eczema affects males and females differently, with higher prevalence among males during childhood that shifts during puberty onwards to affect females more than males [15-17]. Moreover, it has been shown that females bear higher eczema-related DALYs than males [18].

Genetic and environmental factors have been implicated in the pathogenesis of eczema. Variants in the filaggrin gene (*FLG*) have been shown to be the strongest and most consistent genetic risk factor for eczema development [19]. Nonetheless, genetic factors alone do not account for the observed increase in eczema prevalence in recent decades and the within and between countries variations. Such disparities in eczema burden are indicators of the important role of environmental factors, in addition to the genetic elements, in disease pathogenesis.

In Kuwait, a report based on the International Study of Asthma and Allergies in Childhood (ISAAC) methodology conducted among adolescents aged 13–14 years in 2001-2002 estimated a prevalence of 8.3% with respect to current eczema symptoms (i.e., itchy rash in the past 12 months) [20]. Another study conducted in 2015 among young adults aged 18–26 years in Kuwait estimated a higher prevalence of current eczema symptoms, 22.7% [21]. There have been no recent studies on the epidemiology, characteristics, and risk factors of eczema among adolescents in Kuwait. Hence, the current study sought to provide recent prevalence estimates of eczema symptoms and severity among adolescents in Kuwait, describe sex differences in eczema symptoms, determine frequency of sleep disturbance due to itchy rash, use of antihistamines in relation to nocturnal sleep disturbance, and evaluated risk factors (birth-related and environmental conditions).

METHODS

Study setting, design, and participants

Kuwait, a high income country according to the World Bank classification, is a small country located in the Arabian Peninsula. In December 31, 2017, the total population of Kuwait was estimated to be approximately 4.5 million people, and approximately 24.6% of the population is ≤19 years of age. Kuwait is divided geographically into six governorates, and school districts follow a similar geographic division. The education system is divided into four stages, namely, kindergarten, elementary school (1^{st}-5^{th} grade), middle school (6^{th} -9^{th} grade), and high school (10^{th} -12^{th} grade), with schooling being compulsory for all children aged 6 to 14 years.

A school-based, cross-sectional study was conducted by enrolling schoolchildren attending public middle schools from all six school districts in Kuwait. A sample of students was selected from a random sample of middle schools across Kuwait using stratified two-stage cluster sampling. The sampling details have been described previously [*References were removed for blinded peer review*]. The participants were enrolled in the study during the 2016–2017 school year (September 2016 to May 2017) and the first semester of the 2017–2018 school year (September to December 2017). Ethical approval for the current study was obtained from the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait (no. 2016/451). Written informed consent was obtained from parents or legal guardians. The study was conducted in accordance with principles and guidelines of the Declaration of Helsinki for medical research involving human subjects.

Study questionnaire

A study-specific questionnaire and the ISAAC questionnaire [22] were sent home with the children for parental/guardian completion and return. The questionnaires collected information on demographic data, lifestyle factors, environmental exposures, and clinical history and symptoms of allergic disease of both the children and their parents.

Ascertainment of eczema symptoms

Eczema symptoms were defined according to the ISAAC methodology [8]. The presence of a current (i.e., in the past 12 months) itchy rash was determined by asking the following question: "Has your child had this itchy rash any time in the past 12 months?" Moreover, an affirmative response to the question "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes" was used to determine the presence of a current itchy flexural rash. These questions were preceded by the question: "Has your child ever had an itchy rash coming and going for at least six months?" The presence of current symptoms of severe eczema was defined as having a current flexural rash associated with sleep disturbance ≥1 night per week. The presence of ever doctor-diagnosed eczema was assessed by asking whether the child had ever been diagnosed as having eczema by a doctor. According to the criteria defined by Hanifin and Rajka [23], current eczema was defined as "ever doctor-diagnosed eczema" and/or "having ever had a recurrent itchy rash for at least six months" plus "having a current itchy flexural rash."

Assessment of exposure variables and covariates

Body mass index (BMI)-for-age Z-scores (standard deviation [SD]) were calculated according to the World Health Organization (WHO) growth reference for those aged between 5 and 19 years and categorized as follows: underweight (thinness): <-2 SD, normal weight: -2 to 1 SD, overweight: >1 to 2 SD, and obese: >2 SD [24]. Mode of child's birth/delivery (vaginal or cesarean section) and whether the child was ever directly fed at the breast during infancy were reported by the parent/guardian. Moreover, household exposure to environmental tobacco smoke (ETS) was assessed by inquiring whether any member of the household smokes cigarettes or tobacco-related products inside the home. To ascertain exposure to household cats and dogs during infancy, two separate questions were asked: "Did you have a cat/dog in your home during the first year of this child's life?" The child's birth order among his/her siblings born to the same mother was reported as follows: first-born, second-born, third-born, and fourth-born and more. The frequency of antihistamine use was ascertained by asking the following question: "In the past 12 months, how often, on average, has the child taken antihistamine medication (e.g., Zyrtec, Claritin, Aerius)?" Answer options included: never, at least once a year, at least once per month, and don't know. Information on parental history of eczema was obtained by asking the following: "Has the child's mother/father ever been diagnosed with eczema by a doctor?"

The frequency of nocturnal sleep disturbance due to itchy rash was assessed by asking: "In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash?", with answer options being: never, less than one (<1) night per week, and one or more (≥1) nights per week. To assess the persistence of eczema symptoms, the following question was

asked: “Has this rash cleared completely at any time during the past 12 months?” The previous questions were only applicable to children who reported itchy rash in the past 12 months.

Statistical analysis

Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). The statistical significance level was set to $\alpha = 0.05$. Descriptive analyses were conducted to calculate frequencies and proportions of categorical variables. Prevalence of eczema symptoms and severity were estimated along with their binomial 95% confidence intervals (CI). Chi-squared (χ^2) test was used to assess differences in proportions, and the Cochran-Armitage trend test was applied to assess trends in proportions. Additionally, prevalence estimates were sex- and age-standardized according to the direct method of standardization using the 2017 midyear Kuwait population estimates as reference. The STDRATE procedure in SAS 9.4 was used to compute directly standardized prevalence estimates.

Univariate analyses were applied to examine the association of each individual independent variable (exposure variable) with an outcome variable (current eczema status and frequency of nocturnal sleep disturbance). Variables that demonstrated possible association (p-value <0.2) with current eczema status in the univariate analyses were simultaneously entered into a multivariable regression model. Similarly, variables that demonstrated possible association (p-value <0.2) with frequency of nocturnal sleep disturbance in the univariate analysis were simultaneously entered into the multivariable regression model. A modified Poisson regression with robust variance estimation using the GENMOD procedure in SAS 9.4 was applied to estimate and infer adjusted prevalence ratios (aPR) and their 95% CIs [25]. Given that the

nocturnal sleep disturbance variable (outcome variable) has three categories, the "never" category was set as the reference and two regression models (<1 night per week vs. never and ≥1 nights per week vs. never) were evaluated.

In an additional analysis, antihistamine use (never/at least once a year vs. at least once per month) in the past 12 months was considered as an outcome variable and the frequency of nocturnal sleep disturbance due to itchy rash (never, <1 night per week, ≥1 nights per week) was considered as an exposure variable. Trend in antihistamine use according to the frequency of nocturnal sleep disturbance due to itchy rash was assessed. Moreover, aPRs and their 95% CIs relating the frequency of nocturnal sleep disturbance (the 'never' group was set as the reference) to antihistamine use were estimated.

RESULTS

A total of 3,864 (1,695 males and 2,169 females) subjects were enrolled in the study (response proportion: 73.9%, 3864/5228). The study sample included schoolchildren aged between 11 and 14 years old, with a median age of 12 years (Table 1). Based on BMI-for-age categories, 25.3% (961/3786) and 28.8% (1089/3786) of the participants were classified as overweight and obese, respectively. Moreover, of the total study participants, 18.2% (692/3798) were born via cesarean section, 45.8% (1755/3836) were exposed to household ETS, and 76.3% (1755/3792) were ever breastfed. The prevalence of maternal and paternal history of ever doctor-diagnosed eczema was 13.9% (500/3610) and 14.1% (501/3560), respectively (Table 1).

The prevalence estimates of eczema symptoms and severity in the total study sample and stratified by sex are reported in Table 2. Ever doctor-diagnosed eczema was reported by 19.5% of the total study sample, with more males than females reporting ever doctor-diagnosed eczema (22.1% vs. 17.4%, p-value <0.001). Current (past 12 months) itchy rash was reported by 20.5% (735/3593) of the study sample with no difference between males and females. The prevalence of current eczema was estimated to be 10.2% in the total study sample with no sex-related differences. Current symptoms of severe eczema were reported by 8.7% of the participants who had current itchy rash, with no sex-related differences. We also calculated sex- and age-standardized prevalence estimates, which did not differ from the unadjusted estimates (Table 2).

Supplemental Figure 1 shows the prevalence estimates of eczema symptoms and severity according to sex and age groups. The prevalence of current eczema was higher among males than females aged <12 years (13.9% vs. 9.9%, p-value = 0.049). While among subjects aged ≥14

years the prevalence of current eczema was higher among females than males (12.2% vs. 8.8%, p-value = 0.161), though this difference did not gain statistical significance. Similar sex-related differences over age were observed for current itchy rash and current itchy flexural rash. There were no sex-related differences across age groups in symptoms of severe eczema (Supplemental Figure 1). Among males, the prevalence of current itchy rash (P_{trend} <0.001), current itchy flexural rash (P_{trend} = 0.004), and current eczema (P_{trend} = 0.015) demonstrated decreasing trends across age groups. Whereas, among females, there were increasing trends in the prevalence of current itchy flexural rash (age <12: 11.0% vs. age ≥14: 14.2%, P_{trend} = 0.229) and current eczema (age <12: 9.9% vs. age ≥14: 12.2%, P_{trend} = 0.437) across age groups, though these trends were not statistically significant.

Among subjects reporting current itchy rash, frequency of nocturnal sleep disturbance due to itchy rash and persistence of itchy rash were assessed (Table 3). Of those reporting current itchy rash, 21.7% and 12.7% reported being kept awake at night due to itchy rash for <1 night per week and ≥1 nights per week, respectively. With regard to persistence, 31.5% of subjects with current itchy rash reported that their itchy rash has never completely cleared at any time in the past 12 months. There were no sex-related differences in the frequency of nocturnal sleep disturbance and persistence of itchy rash (Table 3).

Table 4 shows associations of different factors with current eczema. Underweight compared to normal weight based on BMI-for-age was associated with increased prevalence of current eczema (aPR = 1.71, 95% CI: 1.16-2.53). Overweight and obesity showed trends for association with increased current eczema prevalence. Cesarean section compared to vaginal delivery was

associated with increased prevalence of current eczema (aPR = 1.29, 95% CI: 1.01-1.65). Maternal (aPR = 1.72, 95% CI: 1.35-2.19) and paternal (aPR = 1.83, 95% CI: 1.44-2.32) history of doctor-diagnosed eczema was associated increased current eczema prevalence (Table 4).

Results of association analysis between different factors and frequency of nocturnal sleep disturbance due to itchy rash among subjects with current itchy rash are shown in Table 5. Subjects aged ≥14 years were more likely to report nocturnal sleep disturbance than those aged <12 years. Moreover, cesarean section delivery was associated with frequent sleep disturbance due to itchy rash (≥1 night per week vs. never: aPR = 1.98, 95% CI: 1.37-2.85). Household exposure to ETS was associated with sleep disturbance for <1 night per week (aPR = 1.40, 95% CI: 1.07-1.85) and ≥1 nights per week (aPR = 1.70, 95% CI: 1.18-2.47). Having a dog was associated with reporting sleep disturbance due to itchy rash for ≥1 nights per week (aPR = 1.93, 95% CI: 1.06-3.52; Table 5).

Figure 1 shows the association between frequency of nocturnal sleep disturbance due to itchy rash and the use of antihistamine at least once per month in the past 12 months among subjects reporting current itchy rash. Among subjects with current itchy rash, 29.3% reported using antihistamines at least once per month in the past 12 months. The use of antihistamine at least once per month increased as the frequency of nocturnal sleep disturbance increased (P_{trend} <0.001, Figure 1). Compared to subjects reporting no nocturnal sleep disturbance, reporting being kept awake by itchy rash for <1 night per week (aPR = 1.55, 95% CI: 1.17-2.05) and ≥1 nights per week (aPR = 2.03, 95% CI: 1.52-2.71) was associated with increased antihistamine use at least once per month (Figure 1).

DISCUSSION

This large school-based cross-sectional study described the epidemiology of eczema among adolescents in Kuwait. The prevalence of current itchy rash and current eczema was estimated to be 20.5% and 10.2%, respectively. Of subjects with current itchy rash, 8.7% reported current symptoms of severe eczema, 34.4% reported nocturnal sleep disturbance due to itchy rash, and 31.5% reported that their itchy rash never completely cleared in the past 12 months. Factors that were associated with current eczema included BMI, mode of birth, and maternal and paternal history of eczema. Factors that were associated with the frequency of nocturnal sleep disturbance included age, mode of birth, household ETS exposure, and dog-keeping. Our findings indicate that eczema affects a considerable proportion of adolescents in Kuwait and different factors influence eczema prevalence.

A study based on the ISAAC methodology conducted in 2001-2002 in Kuwait reported the prevalence of current itchy rash to be 8.3% and ever doctor-diagnosed eczema to be 12.8% among schoolchildren aged 13-14 years [20]. In the current study, both the current itchy rash (20.5%) and ever doctor-diagnosed eczema (19.5%) prevalence estimate are substantially higher than the estimates reported by the aforementioned study. Our estimates are close to prevalence estimates reported in a study conducted in 2015 in Kuwait among young adults aged 18-26 years, which reported the prevalence of current itchy rash to be 22.7% and ever-doctor diagnosed eczema to be 20.2% [21]. Such results suggest that the prevalence of eczema symptoms have increased in the past 20 years in Kuwait. Compared to the results of the Global Asthma Network (GAN) Phase I study among adolescents aged 13-14 years [26], our prevalence estimates of current eczema (10.2%) and ever doctor-diagnosed eczema (19.5%) are comparable to estimates

of high-income countries reported in the GAN study (current eczema symptoms: 9.9%; ever eczema: 20.8%). Moreover, our estimated current eczema prevalence is similar to estimates from the Isle of Wight birth cohort based in the United Kingdom (current eczema at age 10 years: 13.7%) [11] and the German birth cohort, the Multicenter Allergy Study, that showed eczema prevalence to be at around 10% throughout school age [27]. Overall, our results indicate that the eczema prevalence has increased over that past 20 years among adolescents in Kuwait and the current burden of eczema in Kuwait is similar to the burden in western and high-income countries.

We observed a trend to a sex-related switchover in the prevalence of eczema symptoms with age, with higher prevalence among males than females in those aged <12 years and higher prevalence among females than males in those aged ≥14 years. Such an observation of higher eczema prevalence before puberty among males that switches to become more prevalent among females during puberty and onwards has been reported by multiple studies [11, 15-17, 26, 28]. A previous prospective study covering the first 26 years of life showed that females were more likely than males to newly develop eczema during adolescence and early adulthood, and males outgrew eczema more often than females during adolescence [11]. Biologically, this sex-specific development of eczema has been suggested to be influenced by sex hormones (i.e., estrogen and progesterone) that affect the two major hallmarks of eczema, namely immune responses and epidermal barrier function [29].

In the current study, nocturnal sleep disturbance due to itchy rash affected 34.4% (21.7% were affected <1 night per week and 12.7% were affected ≥1 nights per week) of subject with current

itchy rash. A study among Singapore schoolchildren aged 12-15 years reported similar proportions of nocturnal sleep disturbance due to itchy rash, with 29.4% being affected <1 night per week and 11.5% being affected ≥1 nights per week [30]. An investigation among 180 US children aged 5-17 years with eczema estimated that sleep disturbance occurs in 66.9% of subjects, with increased sleep disturbance frequency observed among children with severe disease [31]. Using data from the Avon Longitudinal Study of Parents and Children in the United Kingdom, Ramirez et al. reported that 13.5% of children aged 10 years with active eczema experienced nighttime awakenings (≥1 per night), and showed that children with eczema compared to those without eczema experienced more sleep-quality disturbances [32]. These observations show that eczema symptoms are associated with sleep disruptions and consequently can negatively affect the well-being and health of those affected by the disease. For instance, prior studies have shown that sleep disturbances amongst children and adolescents is associated with cognitive impairments, behavioral problems, and negative impacts on learning and school performance [33-35]. Hence, children with eczema should be screened for sleep disturbances to prevent/manage the health-related consequences.

Factors that showed association in our study with current eczema prevalence included BMI, cesarean section delivery, and maternal and paternal history of eczema. Although prior investigations have reported mixed results for the association between BMI and eczema, a large meta-analysis (30 studies contributing a total of 900,358 subjects) [36] and a systematic review of 45 studies [37] have concluded that majority of the studies reported an association between overweight/obesity and eczema. In line with these observations, when grouping overweight and obese subjects together and comparing them to normal weight subjects, we observed a

statistically significant association with current eczema prevalence (overweight/obese vs. normal weight: aPR = 1.24, 95% CI: 1.02-1.56, data not shown). We additionally found an association between being underweight and current eczema prevalence. This observation is supported by the finding of a previous study that reported an association between underweight and eczema among children (odds ratio (OR) = 4.56, 95% CI: 1.01-20.55) [38]. The corroboration of the observed association between underweight and eczema is hindered by analytical approaches used in most previous studies, which group underweight and normal weight subjects together. Hence, future studies should consider the effect of underweight on the risk of eczema. Moreover, our observation of an increased eczema prevalence among those who were delivered by a cesarean section compared to vaginal delivery is supported by the finding of a meta-analysis of nine studies that reported the prevalence of eczema in cesarean-born infants to be higher than in vaginal-born infants (pooled-OR = 1.31, 95% CI: 1.04-1.65) [39]. This increased risk has been hypothesized to be related to the lack of exposure to maternal vaginal microbiota leading to long-term perturbations in the microbiota composition of newborns, which consequently may affect the development of the immune system [40, 41]. Hence, the effect of cesarean section delivery on allergic diseases development seems to be, at least partially, mediated through alternations in the microbiota. Furthermore, our observation of an association between maternal and paternal history of eczema with child's eczema development is supported by the finding of a meta-analysis that included 9,095 eczema patients and 61,736 reference individuals (parental history of eczema pooled-OR = 3.30, 95% CI: 2.46-4.42) [42]. Parental history of eczema is one of the strongest and most replicated predictors of offspring risk of eczema, which constitutes the effect of genetics, epigenetics, and the shared environment.

In the current study, frequent nocturnal sleep disturbance due to itchy rash was associated with cesarean section delivery, exposure to household ETS, and dog-keeping. Subjects born via cesarean section had increased frequency of night awakenings (≥1 nights per week) due to itchy rash as compared to vaginal-born subjects. Such an observation should be interpreted with caution as this effect might due to the severity of the disease and not directly related to cesarean section delivery. Moreover, we found that exposure to household ETS was associated with increased night awakenings due to itchy rash. Prior research reported association between ETS exposure and eczema risk/prevalence [43, 44], with limited knowledge on ETS exposure and eczema severity. A study by Fotopoulou et al. showed that passive smoke exposure is associated with increased severity of eczema among children [45]. Analyzing data from the national TREATgermany registry, Pilz et al. reported more severe pruritus among smokers compared to non-smokers with eczema. Cigarette smoke contains a multitude of chemicals that can impact the immune system [46] and have direct effect on the skin barrier properties [47], leading to increased eczema risk and severity. Our observation of increased nocturnal sleep disturbance due to itchy rash among children exposed to household ETS is a novel finding that implicates cigarettes smoke compounds in triggering itch that disrupts regular sleep. Moreover, we observed a positive association between dog-keeping and nocturnal sleep disturbance by itchy rash. This observation is corroborated by a study based on the ISAAC Phase III data (329,494 adolescents, aged 13-14 years from 49 countries) that showed an association between dog-keeping and current symptoms of severe eczema [48]. Overall, these observations indicate that perinatal factors and environmental exposures during childhood can affect the intensity of eczema symptoms.

Antihistamines have been prescribed to eczema patients in an attempt to control itch/pruritus, which is considered one of the most distressing symptoms of the disease that disrupts sleep and impacts patients' quality-of-life [49]. Although there is no robust evidence on the effectiveness of antihistamines in controlling eczema symptoms including itch [50] and the discouragement of the American Academy of Dermatology for using antihistamines for the management of eczema symptoms [51], dermatologists and non-dermatologists continue to prescribe antihistamines to a large proportion of patients [51, 52]. In the current report, we showed that antihistamine use was reported by around one third of subjects with current itchy rash and their use increased as the frequency of nocturnal sleep disturbance by itchy rash increased. Hence, these results suggest that some patients regularly use antihistamines with the objective of improving sleep-disrupting symptoms associated with eczema. Moreover, a study of parents of pediatric eczema patients reported that 63% of parents indicated that antihistamine use is helpful in controlling their child's eczema symptoms [53]. Given the inconclusive existing evidence, future investigations are needed to better inform patients about the benefit/harm of using antihistamines for eczema symptoms.

This large school-based cross-sectional study provided knowledge on eczema epidemiology among a representative sample of adolescents in Kuwait. Using the ISAAC methodology to ascertain eczema and its severity symptoms is an added strength to our study. Nonetheless, misclassification due to reporting bias cannot be excluded in large population-based epidemiological studies, which may lead to overestimating or underestimating the true burden of disease. Our estimated prevalence of current eczema (10.2%) is similar to the reported estimate of high-income countries in the GAN study (9.9%) [26]. Such comparability provides an

assurance that reporting bias is not a major concern in the current study. Moreover, large cross-sectional studies are prone to selection bias, specifically non-response bias. However, the sampling methodology and the high response proportion (73.9%) of our study minimize the effect of such bias on the reported results. It is essential to also indicate that our reported cross-sectional (concurrent) associations do not resemble causal associations due to temporal ambiguity between exposure/cause and effect. Nonetheless, also the confidence intervals of some of the evaluated associations are wide, the addressed associations should not be overlooked, but should be assessed in future prospective cohort studies to better understand their role. Despite these limitations, our results provided observational insights on potential effects of different factors for the development, maintenance, and severity of eczema.

In conclusion, this study showed that eczema affects a considerable proportion of adolescents in Kuwait, and that its prevalence seems to have increased in the past 20 years and mirrors prevalence estimates in high-income western countries. We demonstrated that eczema was more common among young adolescent males than females, and it became more prevalent among older adolescent females than males. We also reported that around one third of subjects with current itchy rash reported nocturnal sleep disturbance due to itchy rash, with increased use of antihistamines among subjects with frequent night awakenings. BMI, cesarean section delivery, and maternal and paternal history of eczema were associated with current eczema prevalence. Whereas, cesarean section delivery, household ETS exposure, and dog-keeping showed associations with nocturnal sleep disturbance due to itchy rash. Overall, our study provided epidemiological description of eczema among adolescents in Kuwait and gave insights on potential factors that might be associated with the disease and its consequences.

List of abbreviations

aPR, adjusted prevalence ratio;

BMI, body mass index;

CI, confidence interval;

DALYs, disability-adjusted life years;

ETS, environmental tobacco smoke;

GAN, global asthma network;

GBD, global burden of disease;

ISAAC, International Study of Asthma and Allergies in Childhood;

SD, standard deviation;

WAO, World Health Organization.

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Figure Legends

Figure 1. Antihistamine use according to frequency of nocturnal sleep disturbance due to itchy rash among subjects with itchy rash in the past 12 months. The gray bars represent the frequency (%) of antihistamine use at least once per month in the past 12 months [left y-axis]. The black vertical lines refer to adjusted prevalence ratio (PR) and their associated 95% confidence intervals (CI) [right y-axis]. Adjusted PRs are showing associations between the frequencies of nocturnal sleep disturbance due to itchy rash (exposure variable) and antihistamine use (outcome variable). The "never" nocturnal sleep disturbance group was set as the reference. The dashed horizontal line refers to PR of 1 (null value). Adjusted PRs were adjusted for age, mode of birth, ETS exposure, and dog-keeping. P_{trend} was calculated using the Cochran-Armitage test for trend.

Supplemental Material

Supplemental Figure 1. Prevalence of (A) current (past 12 months) itchy rash, (B) current itchy flexural rash, (C) current eczema, (D) ever doctor-diagnosed eczema, (E) current symptoms of severe eczema using the total sample as a denominator, and (F) current symptoms of severe eczema using subjects with current itchy rash as a denominator stratified by sex and age. *P*-values were calculated using chi-squared test to assess differences between males and females.

586 **Table 1.** Characteristics of the total study sample

Variable	Total study sample (n = 3864)
Sex, n (%)	
Male	1695 (43.9)
Female	2169 (56.1)
Age (years), n (%)	
<12	1065 (27.5)
12 to <13	1170 (30.3)
13 to <14	964 (25.0)
≥14	665 (17.2)
BMI-for-age categories, n (%)	
Underweight (< -2 SD)	219 (5.8)
Normal (-2 to 1 SD)	1517 (40.1)
Overweight (> 1 to 2 SD)	961 (25.3)
Obese (> 2 SD)	1089 (28.8)
Missing, n	78
Mode of birth, n (%)	
Vaginal	3106 (81.8)
Cesarean section	692 (18.2)
Missing, n	66
Breastfeeding ever, n (%)	
Yes	2894 (76.3)
Missing, n	72
ETS exposure, n (%)	
Yes	1755 (45.8)
Missing, n	28
Current household cat, n (%)	
Yes	500 (13.1)
Missing, n	36
Current household dog, n (%)	
Yes	119 (3.1)
Missing, n	28
Birth order, n (%)	
First	1103 (28.7)
Second	801 (20.8)
Third	638 (16.6)
Fourth or more	1302 (33.9)
Missing, n	20
Maternal history of eczema, n (%)	
Yes	500 (13.9)
Missing, n	254
Paternal history of eczema, n (%)	
Yes	501 (14.1)
Missing, n	304

587 BMI: body mass index; SD: standard deviation; ETS: environmental tobacco smoke.

588 **Table 2.** Prevalence of current (past 12 months) itchy rash, current itchy flexural rash, current eczema, ever doctor-
589 diagnosed eczema, current symptoms of severe eczema in the total study sample and stratified by sex

	Prevalence, % (n/total)	95% CI	Sex difference *P*-value*
Current itchy rash			
Total	20.5 (735/3593)	19.1-21.8	
Total - Sex- and age-standardized†	20.2	18.7-21.7	
Males	20.4 (322/1580)	18.4-22.4	0.919
Females	20.5 (413/2013)	18.8-22.3	
Current itchy flexural rash			
Total	11.3 (417/3791)	10.3-12.3	
Total - Sex- and age-standardized†	11.2	10.1-12.4	
Males	11.3 (185/1637)	9.8-12.8	0.954
Females	11.2 (232/2064)	9.9-12.6	
Current eczema			
Total	10.2 (388/3791)	9.3-11.2	
Total - Sex- and age-standardized†	10.2	9.2-11.3	
Males	10.4 (173/1668)	8.9-11.8	0.805
Females	10.1 (215/2123)	8.8-11.4	
Ever doctor-diagnosed eczema			
Total	19.5 (736/3775)	18.2-20.8	
Total - Sex- and age-standardized†	19.6	18.1-21.0	
Males	22.1 (368/1663)	20.1-24.1	<0.001
Females	17.4 (368/2112)	15.8-19.0	
Current symptoms of severe eczema (total participants denominator)			
Total	1.7 (64/3701)	1.3-2.2	
Total - Sex- and age-standardized†	1.8	1.4-2.3	
Males	1.7 (28/1637)	1.1-2.3	0.938
Females	1.7 (36/2064)	1.2-2.3	
Current symptoms of severe eczema (current itchy rash denominator)‡			
Total	8.7 (64/735)	6.6-10.8	
Total - Sex- and age-standardized†	9.5	7.0-11.9	
Males	8.7 (28/322)	5.6-11.8	0.992
Females	8.7 (36/413)	6.0-11.4	

590 CI: confidence interval
591 * Comparing prevalence in males and females using chi-squared test.
592 † Prevalence estimates for the total population were sex- and age-standardized according to the age- and sex-specific
593 population weights of the 2017 midyear Kuwait population estimates.
594 ‡The presented data are restricted to participants who have current (past 12 months) itchy rash (n = 735).
595

Table 3. Frequency of nocturnal sleep disturbance due to itchy rash and persistence of itchy rash among subjects with itchy rash in the past 12 months

	Total		Males		Females		
	Prevalence, % (n/total)	**95% CI**	**Prevalence, % (n/total)**	**95% CI**	**Prevalence, % (n/total)**	**95% CI**	**Sex difference *P*-value***
Kept awake at night by itchy rash in the past 12 months							
Never	65.6 (475/724)	62.2-69.1	65.7 (209/318)	60.5-70.9	65.5 (266/406)	60.9-70.1	0.769
<1 night per week	21.7 (157/724)	18.7-24.7	20.8 (66/318)	16.3-25.2	22.4 (91/406)	18.4-26.5	
≥1 nights per week	12.7 (92/724)	10.3-15.1	13.5 (43/318)	9.8-17.3	12.1 (49/406)	8.9-15.2	
Itchy rash ever cleared in the past 12 months							
No	31.5 (227/720)	28.1-34.9	31.6 (101/320)	26.5-36.7	31.5 (126/400)	26.9-36.1	0.986
Yes	68.5 (493/720)	65.1-71.9	68.4 (219/320)	63.4-73.5	68.5 (274/400)	63.9-73.1	

CI: confidence interval

* Comparing prevalence in males and females using chi-squared test.

Table 4. Factors associated with current eczema: univariate and adjusted associations

	Current Eczema, % (n/total)	*P*-value*	aPR† (95% CI)
Age (years)			
<12	11.9 (125/1047)	0.109	1.00 (Ref.)
12 to <13	9.3 (107/1149)		0.76 (0.59-0.99)
13 to <14	9.1 (85/939)		0.75 (0.56- 0.98)
≥14	10.8 (71/656)		0.85 (0.63-1.16)
BMI-for-age categories			
Underweight (<-2 SD)	14.6 (31/213)	0.078	**1.71 (1.16-2.53)**
Normal (-2–1 SD)	9.1 (136/1488)		1.00 (Ref.)
Overweight (>1–2 SD)	10.8 (102/944)		1.23 (0.94-1.60)
Obese (>2 SD)	10.8 (115/1070)		1.26 (0.97-1.63)
Mode of birth			
Vaginal	9.8 (299/3063)	0.066	1.00 (Ref.)
Cesarean section	12.1 (83/685)		**1.29 (1.01- 1.65)**
Breastfeeding ever			
Yes	9.9 (282/2850)	0.208	1.00 (Ref.)
No	11.4 (101/889)		1.09 (0.86-1.39)
Birth order			
First	10.4 (113/1088)	0.820	
Second	9.8 (78/794)		
Third	9.5 (60/629)		
Fourth or more	10.8 (137/1270)		
ETS exposure			
No	9.0 (185/2047)	0.008	1.00 (Ref.)
Yes	11.7 (202/1730)		1.17 (0.95- 1.44)
Current household cat			
No	9.8 (321/3276)	0.043	1.00 (Ref.)
Yes	12.8 (63/494)		1.18 (0.89-1.57)
Current household dog			
No	10.2 (372/3660)	0.351	
Yes	12.8 (15/117)		
Maternal eczema			
No	9.0 (278/3095)	<0.001	1.00 (Ref.)
Yes	17.3 (86/497)		**1.72 (1.35-2.19)**
Paternal eczema			
No	8.8 (268/3038)	<0.001	1.00 (Ref.)
Yes	17.8 (89/501)		**1.83 (1.44-2.32)**

SD: standard deviation; ETS: environmental tobacco smoke; aPR: adjusted prevalence ratio; CI: confidence interval; Ref: reference.

* Calculated using chi-squared test.

† Adjusted for factors that showed possible association (i.e., p-value <0.2) with current eczema in the univariate analysis, which included age, BMI-for-age, mode of birth, breastfeeding, ETS exposure, cat-keeping, maternal eczema, and paternal eczema.

608 **Table 5.** Factors associated with frequency of nocturnal sleep disturbance due to itchy rash among subjects with
609 itchy rash in the past 12 months: univariate and adjusted associations

	Kept awake at night by itchy rash in the past 12 months			aPR† (95% CI) [<1 night/week vs. Never]	aPR† (95% CI) [≥1 nights/week vs. Never]
	<1 night/week, % (n/total)	≥1 nights/week, % (n/total)	*P*-value*		
Age (years)					
<12	16.7 (38/227)	11.0 (25/227)	0.076	1.00 (Ref.)	1.00 (Ref.)
12 to <13	24.9 (54/217)	12.0 (26/217)		**1.53 (1.06-2.21)**	1.32 (0.78-2.21)
13 to <14	21.7 (35/161)	11.8 (19/161)		1.28 (0.84-1.94)	1.17 (0.67-2.05)
≥14	25.2 (30/119)	18.5 (22/119)		**1.63 (1.07-2.49)**	**1.85 (1.10-3.09)**
BMI-for-age categories					
Underweight (<-2 SD)	22.0 (9/41)	9.8 (4/41)	0.492		
Normal (-2–1 SD)	20.6 (54/262)	16.0 (42/262)			
Overweight (>1–2 SD)	22.5 (41/182)	13.2 (24/182)			
Obese (>2 SD)	21.4 (48/224)	9.4 (21/224)			
Mode of birth					
Vaginal	21.8 (124/570)	10.9 (62/570)	0.010	1.00 (Ref.)	1.00 (Ref.)
Cesarean section	21.5 (31/144)	20.1 (29/144)		1.16 (0.83-1.61)	**1.98 (1.37-2.85)**
Breastfeeding ever					
Yes	22.6 (121/535)	12.2 (65/535)	0.531		
No	19.7 (36/183)	14.8 (27/183)			
Birth order					
First	21.6 (46/213)	12.2 (26/213)	0.864		
Second	23.1 (34/147)	10.9 (16/147)			
Third	17.9 (20/112)	12.5 (14/112)			
Fourth or more	22.7 (57/251)	14.3 (36/251)			
ETS exposure					
No	18.9 (70/370)	9.5 (35/370)	0.001	1.00 (Ref.)	1.00 (Ref.)
Yes	24.5 (86/351)	16.2 (57/351)		**1.40 (1.07-1.85)**	**1.70 (1.18-2.47)**
Current household cat					
No	21.4 (130/607)	12.7 (77/607)	0.977		
Yes	22.3 (25/112)	12.5 (14/112)			
Current household dog					
No	21.7 (152/701)	12.3 (86/701)	0.086	1.00 (Ref.)	1.00 (Ref.)
Yes	19.1 (4/21)	28.6 (6/21)		0.93 (0.39-2.21)	**1.93 (1.06-3.52)**
Maternal eczema					
No	20.4 (110/540)	12.0 (65/540)	0.301		
Yes	25.0 (37/148)	14.2 (21/148)			
Paternal eczema					
No	21.4 (110/514)	13.4 (69/514)	0.241		
Yes	21.9 (34/155)	8.4 (13/155)			

610 SD: standard deviation; ETS: environmental tobacco smoke; aPR: adjusted prevalence ratio; CI: confidence interval;
611 Ref: reference.
612 * Calculated using chi-square test.
613 † Adjusted for factors that showed possible association (i.e., p-value <0.2) with nocturnal sleep disturbance in the
614 univariate analysis, which included age, mode of birth, ETS exposure, and dog-keeping.

Figure