

PREVALENCE OF ATOPIC ECZEMA WITH OR WITHOUT WHEEZE IN KOSOVAR ADOLESCENTS: ROLE OF GENDER, EXERCISE AND PARACETAMOL.

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Abstract

Objectives To characterise the epidemiology of atopic eczema in adolescents from Kosovo, an area of very low prevalence of the condition and to know whether the same factors are associated to eczema with or without comorbid wheezing symptoms. **Methods** The cross-sectional survey Global Asthma Network validated questionnaire was self-completed by adolescents 13-14 years of age in the school setting from the main cities of Kosovo: Ferizaj, Gjakova, Gjiilan, Peja, Prishtina and Prizren. Atopic eczema symptoms and diagnosis was put in relation with the environmental questionnaire which included questions on smoking; pet ownership; paracetamol use, truck traffic; siblings; time spent using screens or watching television; and exercise. Additionally, height and weight were measured at school. **Results** The prevalence of eczema symptoms ranged from 2.2% in Ferizaj to 5.5% in Gjakova. Severe symptoms were <1% in all cities. Eczema ever ranged from 3.0% in Ferizaj to 6.4% in Prizren. Factors significantly associated to the prevalence of current eczema symptoms in the metanalysis were male sex (pooled aOR 0.50; 95%CI 0.37-0.66); exercise (pooled aOR 2.79; 95%CI 1.89-4.10); and paracetamol intake (pooled 1.86; 95%CI 1.32-2.64). The corresponding figures for eczema ever were: 0.68 95%CI 0.44-1.06; 2.07 95%CI 1.48-2.90; and 1.19 95%CI 0.88-1.60. The associations tended to be higher in the subpopulation with eczema and wheeze comorbidity. **Conclusions** The prevalence of atopic eczema is very low in Kosovo and is associated to female sex, exercise, and paracetamol intake. Those associations are higher when eczema and wheezing are comorbid conditions.

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The cross-sectional survey Global Asthma Network validated questionnaire was self-completed by adolescents 13-14 years of age in the school setting from the main cities of Kosovo: Ferizaj, Gjakova, Gjilan, Peja, Prishtina and Prizren. Atopic eczema symptoms and diagnosis was put in relation with the environmental questionnaire which included questions on smoking; pet ownership; paracetamol use, truck traffic; siblings; time spent using screens or watching television; and exercise. Additionally, height and weight were measured at school.

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Conclusions

The prevalence of atopic eczema is very low in Kosovo and is associated to female sex, exercise, and paracetamol intake. Those associations are higher when eczema and wheezing are comorbid conditions.

KEY WORDS

Atopic eczema; Epidemiology; Exercise; Kosovo; Paracetamol.

INTRODUCTION

The prevalence of atopic eczema has increased for the past decades, although the variability of this trend is high and depends in part on the region of the world and on the socioeconomic status¹. According to the last report from the Global Asthma Network (GAN) recently published², the increase in adolescents of 13-14 years has been 0.98% per decade for the last 27 years. In the first GAN survey, carried out between 2015 and 2020, the prevalence in the group of low and middle-low, and on the upper-middle income countries, symptoms of current eczema and lifetime eczema were significantly lower than that of high income countries³. At the time when the survey was performed, Kosovo was in the group of upper-middle income countries⁴. Additionally, Kosovo, although not having direct access to the sea, can be considered a Mediterranean country. This warm and humid area, as compared to others in the world, has shown relatively low prevalence of atopic eczema⁵ with some studies pointing at climate, and in particular the number of sunny hours, as being part of the explanation^{1,6}.

The prevalence of eczema in Kosovo is basically unknown although there has been some epidemiological data in the Balkan area previously. The International Study of Asthma and Allergies in Childhood (ISAAC) phase III (the methodology of which has been used by GAN) reported data from Albania in the age groups of 6-7 and 13-14 years, which was one of the world lowest for current symptoms of eczema⁵. Both in this ISAAC report and in the more detailed one by Zivković et al.⁷ the lowest prevalence of current eczema symptoms in Serbia and Montenegro was found to be in Novi Sad, (north of Serbia). However, neither of the two reports, nor previous ones in the Balkans^{8,9}, included the study of risk or protective factors for eczema at the individual or centre level. To the best of our knowledge, only one study in Croatia has reported epidemiological factors associated to eczema in the Balkan area in adolescents¹⁰. Another one focused on the association of traffic pollution with allergic diseases¹¹.

Thus, the study of the epidemiology, including potential risk or protective factors, of eczema in adolescents in the main cities of a country such as Kosovo could add important information on the subject: it would show the current size of the problem in an area which has previously presented low prevalence of the condition; may add information about the epidemiological factors in a low prevalence region in order to facilitate comparison with areas of higher prevalence; could allow for comparisons between centres in the same low-prevalence area; and might show paths for prevention.

METHODS

The methods of the GAN study have been already published elsewhere¹² and are mainly identical to those of ISAAC. GAN is cross-sectional study based on written questionnaires distributed in schools in the participating centres. In Kosovo, the survey included the age group of 13-14-years; and six centres: Ferizaj, Gjakova, Gjilan, Peja, Prishtina and Prizren. The fieldwork was carried out between 2017 and 2018.

Questionnaires

The definitions of indicators of atopic eczema were derived from the written questionnaires completed by adolescents at school. The original questionnaire was in English, and translation and back-translation to Albanese followed a specific methodology common to ISAAC and GAN¹³

Definitions

“Current eczema symptoms” was defined as a positive answer to two questions: “Have you had this itchy rash (as defined in a previous question) at any time in the past 12 months?” and “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?”. “Severe eczema symptoms” was defined as symptoms of current eczema being the cause of awakening one or more times per week in the question: “In the past 12 months, how often, on average, have you (has this child) been kept awake at night by this itchy rash? (Never in the past 12 months, less than one night per week, one or more nights per week). “Eczema ever” was defined as a positive answer to: “Have you ever had eczema?”.

“Current wheeze” was defined by a positive answer to the question “Have you (has your child) had wheezing or whistling in the chest in the past 12 months? Current wheeze was used to stratify eczema markers in some of the statistical analyses.

Additionally, adolescents responded to the environmental questionnaire. This included questions on smoking; pet ownership; paracetamol use, truck traffic in the street where adolescents lived; siblings; time spent using screens or watching television; and exercise. Additionally, height and weight were measured at school by fieldworkers in a standardised way according to GAN methods¹². Exercise was assessed by the question “How many times a week do you engage in vigorous physical exercise activity long enough to make you breath hard? (Never or occasionally; once or twice per week; three or more times per week)”. Paracetamol intake was surveyed by the question: “In the past 12 months, how often, on average, have you taken paracetamol for fever? (Never; At least once a year; At least once per month)”. Overweight was defined as body mass index above 25.

Sample size and study power

As for any GAN centre, all students (selected by grade or by age) of 13-14 years within all schools (Ferizaj, Gjakova, Gjilan, Peja, and Prizren) or within a random sample of them (Prishtina) were invited to participate to achieve the minimum required sample size of 1000. Additional details of the sample size and power are described elsewhere^{12,14} Participation rates in Kosovo (80.0% or more) have been also described in detail previously¹⁵.

Statistical analysis

To calculate participation rates, the denominator was the number of adolescents and the numerator the number of core questionnaires returned with at least one data symptom. For prevalence estimations, positive answers to a specific symptom in the centre was divided by the number of completed questionnaires. There was no data imputation.

All variables included in the GAN environmental questionnaire were used as independent variables in logistic regression analyses (uni and multivariate) in which the three eczema markers (current symptoms, severe symptoms, and current eczema) were the dependent variables. Those analyses were performed within each centre. As the number of cases of severe symptoms was very low, logistic regression analyses were not performed. Factors which showed significant ($p < 0.05$) values of adjusted odds ratios in the multivariate logistic regression analyses in at least one centre were subsequently meta-analysed (random effects) including the results of the six centres. A forest plot was built, including the pooled effect together with the 95% confidence interval and prediction interval. Measures of heterogeneity, such as Q and I^2 were also calculated.

To test whether the presence of current wheeze modified the associations between the environmental factors and the eczema markers on the whole sample of adolescents, a multilevel mixed effects logistic regression model was performed, including the same variables as in the within centre logistic regressions; and using the individual as the first level and the centre at the second. As previously and due to the low number of cases, no analysis was made for symptoms of severe eczema.

Most statistical calculations were made using Stata SE® v18 software package (Stata corp., College Station, TX, USA) except meta-analyses that were carried out using Comprehensive Meta-Analysis (CMA) V4.0 software package (Biostat, Englewood, NJ, USA).

Ethics

Prior to the beginning of the study, permission was asked and authorisation issued by the education authorities in each municipality. Passive informed consent was used. The study was approved by the Ethics' Committees of both the Ministry of Health and the Ministry of Education of Kosovo according to the Helsinki declaration (approval No. 21/550).

RESULTS

Demographic and environmental characteristics of the 6 Kosovar centres have been already described¹⁵. Table 1 shows the prevalence of current eczema symptoms, severe eczema symptoms and eczema ever overall, and with and without wheeze, together with the respective 95% confidence intervals. The lowest prevalence of current eczema symptoms occurred in Ferizaj while the highest was in Gjakova. Eczema ever was lowest in Ferizaj again and highest in Gjakova. Overall, the proportion of adolescents with eczema and wheezing symptoms was much lower than that with only eczema symptoms. The prevalence of severe eczema symptoms was very low and similar among the centres.

Web tables 1 and 2 include the associations found in the univariate and multivariate logistic regressions of the different factors with current eczema symptoms and eczema ever, respectively, per centre. Those factors that were consistently associated with current eczema symptoms or eczema ever in most centres were sex, exercise, and paracetamol intake. Forest plots of those three factors showed a trend that male sex (figure 1) was associated to lower prevalence of eczema: pooled aOR=0.49; 95%CI 0.37-0.66, for current eczema; and pooled aOR=0.68; 96%CI 0.44-1.06, for eczema ever.

Figure 2 shows that exercise was associated to higher prevalence of current eczema symptoms and eczema ever, with no apparent dose-effect relationship. The pooled aOR and 95%CI for any frequency of exercise was 2.79 (1.89-4.10) and 2.07 (1.48-2.90) respectively for current eczema symptoms and eczema ever.

Contrary to exercise, paracetamol intake seemed to have a dose-response pattern of association, especially for current eczema symptoms. The pooled aOR and 95%CI were 1.33 (0.81-2.16) and 2.64 (1.61-4.33) for the intake of "at least once a year" and of "at least once a month", respectively. The corresponding figures for eczema ever were: 1.09 (0.75-1.58) and 1.37 (0.85-2.22) (figure 3).

According to the results of the multilevel analyses, stratification by wheeze did not change the patterns of associations, although in those children who suffered from skin plus respiratory symptoms those associations seemed to be stronger. However, the low number of children in the eczema and wheeze group was considerably lower than in the group with eczema without wheeze, making comparisons problematic (table 2).

DISCUSSION

In this cross-sectional epidemiological study on atopic eczema in Kosovo, within the GAN collaboration, we have found very low prevalence of any of the three atopic eczema markers as compared with other GAN centres. In fact, only three centres, two in India (Lucknow, 1.9% and Mysuru, 1.4%) and the one in Sri-Lanka (Anuradhapura, 1.1%) had lower prevalence of symptoms of current eczema than Ferizaj (2.2%); and this centre had the lowest prevalence of severe eczema symptoms, with only five cases in the whole population surveyed (<0.5%). With respect to eczema ever, only nine into sixteen Mexican centres and one Indian (Mysuru) had a prevalence lower than 3.0%, the one found in Ferizaj. The centre with the highest prevalence of those markers in Kosovo is Gjakova with 5.5%, 0.7% and 6.8% respectively for current eczema symptoms, severe eczema symptoms, and eczema ever. Those figures are also quite low as compared to the rest of GAN centres³.

Although there has not been any other previous study on the epidemiology of atopic eczema in Kosovo, there have been some in the Balkan region. In the ISAAC phase III survey⁵, carried out around 2002, Tiranë (Albania) reported the prevalence of eczema markers defined as in the present study as follows: current eczema symptoms, 2.0%; severe eczema symptoms, 0.2%; and eczema ever, 2.9%, respectively. Furthermore, the corresponding figures for Rijeka (Croatia) and Skope (Republic of Macedonia) were 2.9%, 0.2% and 8.5%;

and 2.7%, 0.3% and 3.7%, respectively. There were also data from five centres in Serbia and Montenegro, which ranged 2.8%-8.0%, 0.5%-1.3%, and 8.2-17.9%, respectively. The report by Zivković et al.⁷ on Serbia and Montenegro expands further the data included in the ISAAC phase III report and showed low prevalence rates of other eczema markers.

Apart from offering the first epidemiological data on atopic eczema in Kosovo it is also interesting to study epidemiological factors which might be associated to this condition in a geographical area with very low prevalence where, to the best of our knowledge, those factors have not been yet studied among adolescents. Of those studied factors in the meta-analyses of the six centres, male sex is independently associated to both a significant lower prevalence of current eczema symptoms and of eczema ever (if Prizren is excluded in the latter case) (figure 1). The prevalence of severe eczema symptoms is too low to allow any multivariate statistics. The influence of sex in atopic eczema has been previously studied in adolescents in the Balkan area: Stipic-Markovic et al.⁹ found no association between eczema markers and sex in Zagreb among adolescents included in the ISAAC phase III survey. However, other studies have found that different eczema markers are significantly more prevalent in female sex in this age group, like that by Mercer et al. carried out in Cape Town (South Africa)¹⁶. In the EPI-CARE study, a recent international cross-sectional study in children (6 months to <12 years old) and adolescents (12 to <18 years old) using ISAAC methods and defining atopic dermatitis with the same criteria as in the present study found that prevalence differences by sex, in one or the other direction, existed in some countries but not in others¹⁷. However, the authors did not report those differences separately in the two age groups studied. In the BAMSE study, a longitudinal population-based cohort study, carried out in Stockholm, the follow-up visit at age 11-14 years did show a significantly higher prevalence among females when using an eczema questionnaire specifically designed for the study¹⁸. The same was found in a large international cross-sectional study among adults 18–65 years old¹⁹, and previously in a Swedish study on individuals 17-75 years of age which used the GA²LEN questionnaire to assess eczema symptoms²⁰. These findings are shared by other studies^{21,22}. A recent BAMSE report after the visit at 24 years of age of the individuals in the cohort, further extends the finding of male sex is associated to lower prevalence of eczema markers²³. Sex hormones seem to play a role in this difference after puberty²⁴. Current eczema symptoms and eczema ever were also associated to exercise in an apparently not dose-response fashion. Making regular exercise was significantly associated with the increase of prevalence of both atopic eczema markers overall, although this was not the case in some of the centres (figure 2).

As found in the present study, exercise has been associated to eczema previously, although the information is quite limited. In a systematic review and metaanalysis by Kim et al.²⁵ in 2016 only seven manuscripts were included after searching all relevant literature databases since their existence. Three studies found some association between exercise and eczema; three showed an inverse relationship and one did not find any association. Only five of them had enough data to be included in metaanalysis which yield non-significant summary effects, but interestingly, the only study in adolescents²⁶ showed a significant positive association. Both the two other studies (not included in the metaanalysis) which found positive associations were also performed in children or adolescents^{27,28}. Only one of the studies showing no association was in adolescents. It should be noted that this one only included 481 individuals²⁹. All those studies in adolescents and children used the ISAAC methodology, which requires a sample size of 3000. More recent studies offer additional information. For instance, Jago et al.³⁰, using accelerometers in a ALSPAC population of 6473 adolescents, concluded that the number of minutes of vigorous exercise is not related either to asthma or to eczema, but it is inversely associated to obesity. The nature of the ISAAC studies (cross-sectional) vs. de ALSPAC (longitudinal) and the different ways of measuring exercise (simple questionnaire vs. accelerometer) can explain the discrepancy. However, it cannot be ruled out that low to moderate exercise is associated to higher prevalence of eczema, while moderate to vigorous is not. It well might be that low intensity exercise with skin exposure to environment and climate aggression and sweat could facilitate mild eczema flares in not highly predisposed individuals; and, in contrast, those highly predisposed avoid vigorous exercise to escape from severe flares. In fact, higher disease severity is associated with decreased levels of physical activity secondary to itch, in adults, has been previously shown³¹. The curve of the association between the amount of exercise and the severity of eczema (and thus, awareness in self-reported surveys) might have an inverted

U shape.

On the other hand, Honjo et al.³² found a positive independent association of exercise induced wheeze with eczema in a group of 12,405 asthmatic children 6 to 18 years of age following ISAAC definitions. This is probably in keeping with our findings that the association of exercise with eczema is higher in those adolescents who also reported current wheeze (table 2). We cannot say whether the proportion of atopy was higher in the individuals who wheeze than in those who did not wheeze, but this possibility cannot also be ruled out.

The third variable that was consistently associated to eczema markers was taking paracetamol, both at least once last year and at least once last month (figure 3). This was more consistent for current eczema symptoms than for eczema ever and was probably driven by those individuals who have both eczema and wheeze (table 2). There have been several reports linking the use of paracetamol with eczema, even showing that this association is higher when several allergic diseases coexist³³⁻³⁶. Thus, it cannot be said whether the association between paracetamol and eczema might be driven by asthma and/or rhino-conjunctivitis and/or allergy. The present study shows that the association with frequent use (at least one last month) holds even among those adolescents without current wheeze, but only for current symptoms of the condition. The effect of early paracetamol intake on eczema in children 6-7 years of age with neither asthma nor rhino-conjunctivitis symptoms, has been previously shown³⁷. This probably indicates that the drug impairs the antioxidant system which is crucial to maintain skin integrity after aggression³⁸.

The present study has a main weakness which is its cross-sectional nature, precluding to obtain any causal relationship. On the other hand, the study was conducted using validated methods, on a quite large sample with high participation rate, which is representative of the whole country of Kosovo. It has the additional interest of being an area with quite low prevalence of atopic eczema.

In summary, this study shows that, in an area of low prevalence of atopic eczema, both sex, exercise and paracetamol intake are associated to the number of eczema cases, also in those adolescents without current asthma symptoms. Male sex is associated to lower prevalence while mild to moderate exercise and frequent use of paracetamol are associated to higher prevalence of the condition.

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Conflict of interests

The authors declare no conflict of interest.

Data sharing

The study protocol including a recommended informed consent form and statistical analysis plan are in the public domain. The GAN Phase I data, including de-identified individual participant data, will be made available on the Global Asthma Network website <http://www.globalasthmanetwork.org/> within 12 months

of all GAN Phase I analyses being published. Access will require a formal request, a written proposal and a signed data access agreement.

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Table 1. Prevalence of current eczema symptoms, severe eczema symptoms and eczema ever, overall and with and without wheezing in six Kosovar cities (% and 95% Confidence Interval)⁺

	FERIZAJ N=890	GJAKOVA N=676	GJILAN N=1200	PEJA N=1433	PRISHTINA N=1056	PRIZREN N=1427
Current eczema symptoms	2.2 (1.5-3.5)	5.5 (4.0-7.5)	4.1 (3.1-5.4)	5.0 (4.0-6.3)	5.3 (4.1-6.8)	4.6 (3.6-5.8)
Without wheeze	2.0 (1.3-3.2)	5.3 (3.9-7.3)	3.2 (2.3-4.4)	3.6 (2.8-4.7)	4.1 (3.1-5.5)	3.7 (2.8-4.8)
With wheeze	0.2 (0.06-0.9)	0.2 (0.02-1.1)	0.9 (0.5-1.7)	1.5 (1.0-2.3)	1.3 (0.7-2.2)	1.0 (0.6-1.7)
Severe eczema symptoms	0 ⁺⁺	0.7 (0.3-1.8)	0.6 (0.3-1.2)	0.6 (0.3-1.1)	0.5 (0.2-1.1)	0.6 (0.3-1.1)
Without wheeze	0 ⁺⁺	0.6 (0.2-1.6)	0.5 (0.2-1.1)	0.4 (0.2-0.9)	0.4 (0.1-1.0)	0.4 (0.2-0.9)
With wheeze	0 ⁺⁺	0.1 (0.02-1.1)	0.08 (0.01-0.6)	0.1 (0.04-0.6)	0.1 (0.01-0.7)	0.1 (0.04-0.6)
Eczema ever	3.0 (2.1-4.4)	6.8 (5.1-9.0)	4.2 (3.2-5.5)	5.7 (4.6-7.0)	4.0 (3.0-5.3)	6.4 (5.3-7.8)
Without wheeze	2.4 (1.6-3.6)	6.0 (4.4-8.0)	3.4 (2.5-4.6)	4.7 (3.7-5.9)	3.7 (2.7-5.0)	5.1 (4.1-6.4)
With wheeze	0.7 (0.3-1.5)	0.9 (0.4-2.1)	0.8 (0.4-1.5)	1.1 (0.7-1.8)	0.3 (0.1-0.9)	1.5 (0.1-2.3)

⁺See text for definitions.

⁺⁺No cases.

Table 2. Associations (adjusted⁺ odds ratios) and their 95%CI (in parenthesis) between sex, exercise, and paracetamol intake with current eczema symptoms (upper panel) and eczema ever (lower panel) in six Kosovar cities in the mixed effects multilevel logistic regression analyses.

Current eczema symptoms

	Overall	With wheeze	Without wheeze
Male sex	0.52 (0.39-0.68)	0.52 (0.39-0.71)	0.50 (0.27-0.92)
Exercise			
Never or occasionally	1	1	1
Once or twice per week	2.59 (1.97-13.41)	2.22 (1.65-3.00)	6.10 (2.90-12.4)
Three or more times per week	3.11 (2.14-4.53)	2.30 (1.47-3.57)	10.0 (4.47-22.5)

Paracetamol in the last 12 months			
Never	1	1	1
At least once	1.50 (0.98-2.30)	1.34 (0.85-2.10)	3.70 (0.84-16.3)
At least once per month	2.75 (1.81-4.17)	2.39 (1.54-3.72)	7.16 (1.69-30.5)
Eczema ever	Eczema ever	Eczema ever	Eczema ever
	Ever	With wheeze	Without wheeze
Male sex	0.72 (0.56-0.92)	0.69 (0.52-0.90)	0.88 (0.50-1.56)
Exercise			
Never or occasionally	1	1	1
Once or twice per week	1.68 (1.29-2.19)	1.56 (1.17-2.09)	2.31 (1.27-4.19)
Three or more times per week	2.04 (1.40-2.97)	1.78 (1.16-2.74)	3.32 (1.57-7.00)
Paracetamol last 12 months			
Never	1	1	1
At least once	1.16 (0.83-1.62)	1.14 (0.80-1.64)	1.29 (0.53-3.10)
At least once per month	1.44 (1.02-2.03)	1.29 (0.88-1.88)	2.34 (1.00-5.47)

⁺Adjusted for all the variables in the table, and for age, screen and television time, siblings, truck frequency, cat and dog ownership, tobacco smoking, vaping and overweight.

Figure legends

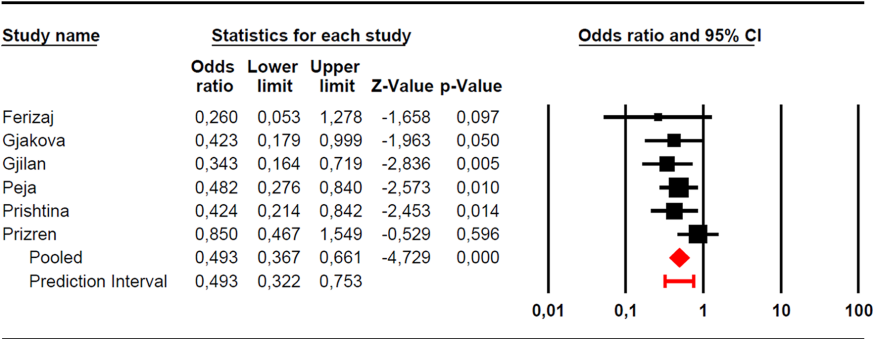
Figure 1. Forest plot of the random meta-analysis of the association of sex with current eczema symptoms (flexural itchy rash -upper panel) and eczema ever (lower panel). $Q=5.03$, $p=0.412$; $I^2=0.68\%$, and $Q=13.7$, $p=0.018$; $I^2=63.5\%$, respectively.

Figure 2. Forest plot of the random meta-analysis of the association of exercise with current eczema symptoms (flexural itchy rash -upper panel) and eczema ever (lower panel). $Q=24.34$, $p=0.011$ (overall); $I^2=54.81\%$ (overall); and $Q=24.31$, $p=0.011$; $I^2=54.75\%$, respectively.

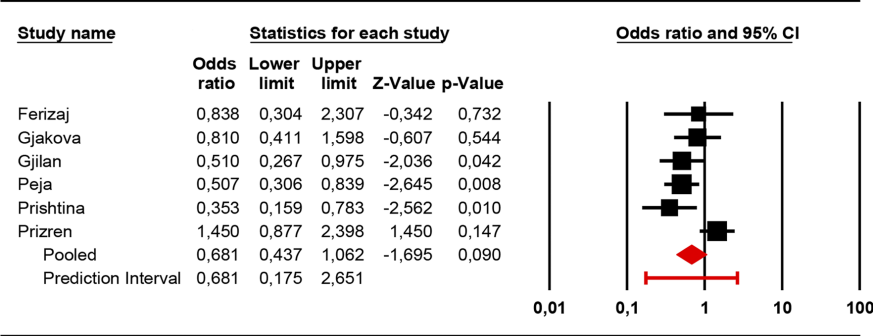
Figure 3. Forest plot of the random meta-analysis of the association of paracetamol intake with current eczema symptoms (flexural itchy rash -upper panel) and eczema ever (lower panel). $Q=16.31$, $p=0.130$ (overall); $I^2=32.57\%$ (overall); and $Q=12.26$, $p=0.344$; $I^2=10.29\%$, respectively.

Current eczema by male sex

Fig 1

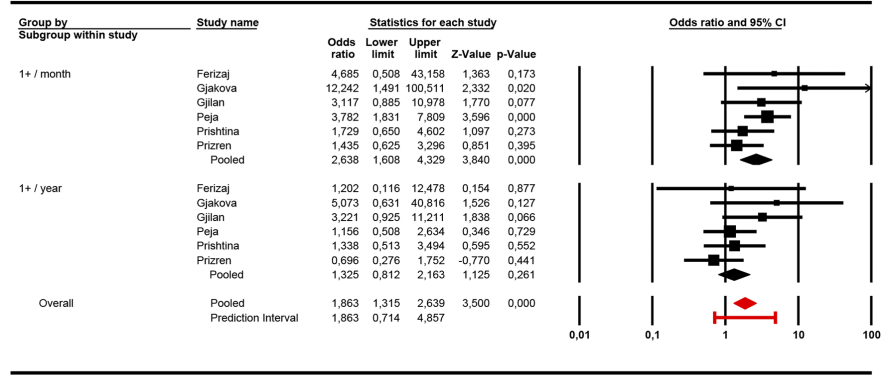


Eczema ever by male sex

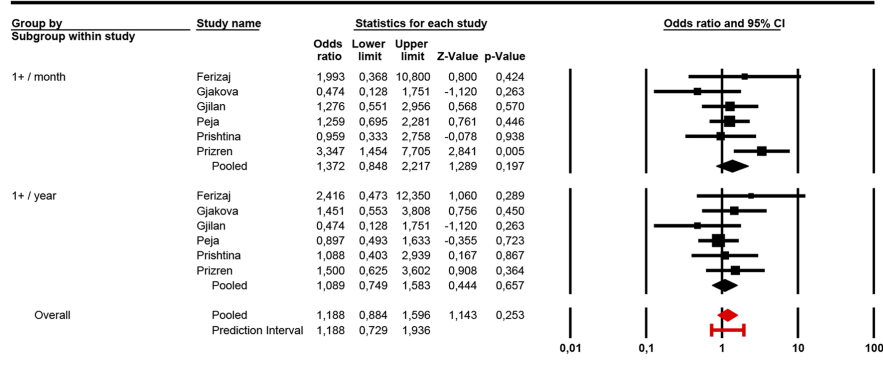


Current eczema by paracetamol use

Fig 3

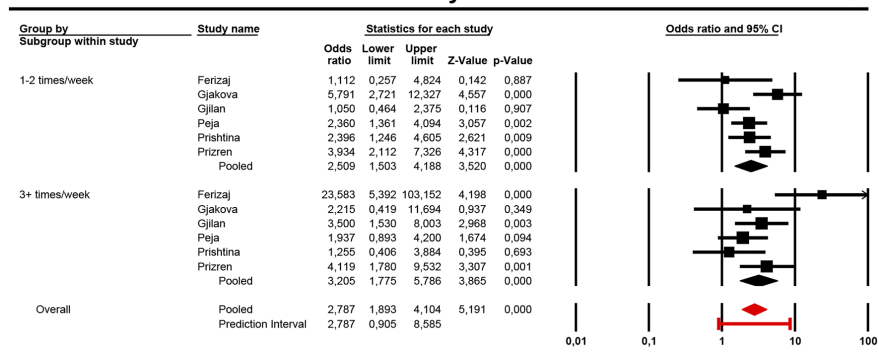


Eczema ever by paracetamol use



Current eczema by exercise

Fig 2



Eczema ever by exercise

