**Table II.** Univariate and multivariate logistic regression models of factors associated with utilization of MMS

| Variable | Univariate (95% CI)* | *P* value | Multivariate (95% CI)* | *P* value |
|---|---|---|---|---|
| Age | 0.980 (0.965-0.994) | .006 | 0.984 (0.962-1.006) | .157 |
| Sex | | | | |
| Male | 1.0 | | 1.0 | |
| Female | 1.312 (0.901-1.912) | .156 | 1.252 (0.845-1.855) | .263 |
| Radiation | | | | |
| No | 1.582 (0.949-2.637) | .079 | 1.655 (0.972-2.819) | .63 |
| Yes | 1.0 | | 1.0 | |
| Charlson-Deyo score | | | | |
| 0 | 2.282 (1.223-4.258) | .009 | 2.134 (1.127-4.041) | .020 |
| ≥1 | 1.0 | | 1.0 | |
| Insurance | | | | |
| Private | 1.771 (1.205-2.602) | .004 | 1.266 (0.718-2.234) | .415 |
| Medicare | 1.0 | | 1.0 | |
| Other | 1.171 (0.524-2.618) | .701 | 0.924 (0.372-2.294) | .865 |
| Facility type | | | | |
| Academic | 1.759 (1.202-2.576) | .004 | 1.645 (1.109-2.439) | .013 |
| Not academic | 1.0 | | 1.0 | |
| Primary site | | | | |
| Head and neck | 2.837 (1.561-5.155) | .001 | 3.259 (1.758-6.041) | <.001 |
| Other | 1.0 | | 1.0 | |

*CI*, Confidence interval; *MMS*, Mohs micrographic surgery.
*Data reported as odds ratio (95% confidence interval).

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## Association of acetaminophen exposure with increased risk of eczema in children: A meta-analysis

*To the Editor:* Many studies[1-5] have assessed the relationship between acetaminophen exposure and the risk of development of eczema (atopic dermatitis) in children. However, the results remain controversial. Here we report a meta-analysis to evaluate the potential association between acetaminophen exposure and the risk of development of eczema in children.

We used the EMBASE, PubMed, and Cochrane Library databases to conduct a meta-analysis of studies published before September 29, 2018, and written in English. The search for studies related to acetaminophen was performed by using the key words and subject terms: *acetaminophen*, *paracetamol, Panadol,* and *Tylenol*, using OR to link the relevant text within the search field. To acquire studies related to eczema, OR was used to associate the key words, which included *dermatitis*, *eczema*, *neurodermatitis*, and *dermatitis, atopic*. We combined these terms using AND to retrieve the relevant studies. Animal studies, studies with adult participants, reports with no indication of the association between acetaminophen and eczema, duplicated reports, case reports, reviews, and meta-analyses were excluded.

Two reviewers (D.X. and X.S.) performed data extraction, evaluated the methodologic quality of the included reports with the Newcastle-Ottawa scale, and discussed disagreements to reach a consensus.

The literature search yielded 314 reports. In total, 15 reports with 901,875 participants were included (see https://data.mendeley.com/datasets/kjbx2v3w6z/1/files/958a9e46-adbc-42c2-92c5-1e9876aa960a/Table%201%20of%20Research%20letter%20of%20JAAD.docx?dl=1). According to the random effects model, acetaminophen exposure increased the risk of eczema (odds ratio [OR], 1.41; 95% confidence interval [CI], 1.23-1.62; $P < .05$) in children. Children exposed prenatally to acetaminophen did not seem to have increased risk of eczema (OR, 1.31; 95% CI, 0.97-1.76; $P > .05$), and children exposed to acetaminophen during the most recent year seemed to have the greatest risk of eczema

**Table I.** Results of stratified analysis of the association between acetaminophen exposure and the risk of eczema in children

| | Prenatal acetaminophen exposure | | | | Acetaminophen exposure in early life (age, ≤1 y) | | | | Acetaminophen exposure during the most recent year (age, >1 y) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Studies** | **OR (95% CI)** | **$I^2$ ($P$ value)** | ***P* value** | **Studies** | **OR (95% CI)** | **$I^2$ ($P$ value)** | ***P* value** | **Studies** | **OR (95% CI)** | **$I^2$ ($P$ value)** | ***P* value** |
| Total | 3 | 1.31 (0.97-1.76) | 0 (.37) | >.05 | 8 | 1.21 (1.04-1.40) | 0.84 (<**.05**) | <**.05** | 9 | 1.70 (1.50-1.92) | 0.82 (<.01) | <**.05** |
| Study location | | | | | | | | | | | | |
| Single country | 3 | 1.31 (0.97-1.76) | 0 (.37) | NA | 7 | 1.18 (1.0-1.41) | 0.81 (<.0001) | >**.05** | 8 | 1.65 (1.37-1.98) | 0.84 (<**.05**) | <**.05** |
| Multiple countries | 0 | NA | NA | | 1 | 1.35 (1.26-1.45) | NA | | 1 | 1.90 (1.78-2.03) | NA | |
| Sample size | | | | | | | | | | | | |
| <10000 | 2 | 1.05 (0.65-1.08) | 0 (.45) | <**.05** | 5 | 1.13 (0.95-1.35) | 0.71 (.008) | <**.05** | 6 | 1.43 (1.30-1.58) | 0 (.53) | <**.05** |
| ≥10000 | 1 | 1.51 (1.03-2.21) | NA | | 3 | 1.31 (1.06-1.62) | 0.84 (.002) | | 3 | 1.98 (1.88-2.08) | 0.28 (.25) | |
| Study design | | | | | | | | | | | | |
| Cohort | 3 | 1.31 (0.97-1.76) | 0 (.37) | NA | 8 | 1.21 (1.04-1.40) | 0.84 (<**.05**) | NA | 6 | 1.74 (1.42-2.13) | 0.84 (<.0001) | >.05 |
| Cross-sectional | 0 | NA | NA | | 0 | NA | NA | | 3 | 1.60 (1.22-2.10) | 0.82 (.003) | |
| Acetaminophen exposure at different dosage and frequency | | | | | | | | | | | | |
| Once/y | 0 | NA | NA | >.05 | 2 | 1.19 (1.10-1.28) | 0 (.71) | <**.05** | 3 | 1.29 (1.21-1.37) | 0 (.63) | <**.05** |
| At least once/mo | 1 | 1.04 (0.65-1.66) | NA | | 2 | 1.73 (1.58-1.89) | 0.86 (<**.05**) | | 7 | 1.76 (1.67-1.85) | 0.8 (<**.05**) | |
| Other | 3 | 1.31 (0.97-1.76) | 0 (.37) | | 6 | 1.13 (1.05-1.22) | 0.83 (<**.05**) | | 1 | 1.81 (1.24-2.64) | NA | |
| Diagnostic eczema at different ages | | | | | | | | | | | | |
| <3 y | 2 | 1.23 (0.72-2.09) | 0.48 (.16) | >.05 | 3 | 1.18 (1.04-1.34) | 0.62 (.07) | <**.05** | 2 | 2.02 (1.92-2.13) | 0 (.65) | <**.05** |
| 3-7 y | 1 | 1.24 (0.65,2.37) | NA | | 5 | 1.25 (1.18-1.32) | 0.92 (<**.05**) | | 4 | 1.56 (1.40-1.74) | 0.75 (<**.05**) | |
| >7 to 18 y | 0 | NA | NA | | 1 | 2.05 (1.61-2.61) | NA | | 4 | 1.84 (1.73-1.95) | 0.75 (<**.05**) | |
| Adjustment factors | | | | | | | | | | | | |
| Unadjusted estimates | 1 | 1.24 (0.65,2.37) | NA | >.05 | 3 | 1.31 (1.23-1.39) | 0.67 (.05) | >.05 | 5 | 1.57 (1.41-1.74) | 0.69 (.01) | <**.05** |
| Adjusted | 2 | 1.23 (0.72-2.09) | 0.48 (.16) | | 5 | 1.26 (1.12-1.41) | 0.70 (<**.05**) | | 4 | 1.94 (1.86-2.01) | 0.83 (<**.05**) | |

Boldface indicates statistical significance.
*CI*, Confidence interval; *NA*, not available; *OR*, odds ratio.

(OR, 1.70; 95% CI, 1.50-1.92; $P < .05$). In addition, children exposed to acetaminophen in early life seemed to have increased risk of eczema (OR, 1.21; 95% CI, 1.04-1.40; $P < .05$). We conducted separate stratified analyses based on study location (single country or multiple countries), study design (cohort study or cross-sectional study), sample size (<10,000 or ≥10,000), acetaminophen exposure at different doses and frequencies (once per year, at least once per month, or other), eczema diagnosed at different patient ages (age, <3 years, 3-7 years, or >7 to 18 years), and whether the study controlled for potential confounders (unadjusted estimates or adjusted estimates) (Table I). Factors explaining differences in the study included sample size, different dosages and durations of acetaminophen use, different patient ages at the diagnosis of eczema, and whether the studies adjusted for potential confounders (Table I).

Our meta-analysis has some limitations, such as publication bias and incomplete ascertainment of the relevant published studies. There are also some potential confounding factors, such as viral infections (which themselves could be a trigger for eczema), recall bias, and diagnosis of eczema based on parental reporting. Therefore, further investigation, including via randomized controlled studies, is needed to establish the exact association and mechanisms.

There are also some merits of our meta-analysis. First, the study featured a large sample that originated from multiple countries, which enhanced its statistical power. Second, we used a stratified analysis in the present study, which helped us to reveal the sources of the heterogeneity.

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## Low-dose naltrexone therapy in benign chronic pemphigus (Hailey-Hailey disease): A case series

*To the Editor:* Familial benign chronic pemphigus, or Hailey-Hailey disease (HHD), is an autosomal-dominant genodermatosis. Treatment of HHD is challenging. Small case series have described the effectiveness of low-dose naltrexone (LDN).[1-3] We assessed the use of LDN in a larger series of patients with HHD.

Patients with biopsy-proven, refractory HHD controlled at the Dermatology Department of Hospital Clínic de Barcelona from November 2017 to November 2018 were proposed to receive LDN. The Institutional Review Board approved the study and written informed consent was obtained from all patients. Starting doses varied from 1.5 to 6 mg/d. Incremental doses were indicated depending on the clinical response (Table I). In some patients who were