

REVIEW ARTICLE

Atopic dermatitis and alcohol use – a meta-analysis and systematic review

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Abstract

While several maternal exposures have been associated with an increased risk of atopic dermatitis (AD) in offspring, the effect of alcohol use during pregnancy on the risk of AD in offspring is unclear. Furthermore, it is unclear whether adults with AD have an increased alcohol use, although other poor health behaviours have been associated with AD including smoking and physical inactivity as well as psychiatric disease. In this systematic review and meta-analysis, the association between alcohol use and AD was investigated in two ways: 1) whether alcohol use (drinkers versus abstainers) during pregnancy is associated with AD in offspring and 2) whether AD is associated with increased alcohol use. The medical databases PubMed, EMBASE and Web of Science were searched, and data extraction was carried out by two independent reviewers. Eighteen studies were included in the qualitative analysis (comparing alcohol drinkers to abstainers), and 12 studies were included in the quantitative analysis. There was a positive association between alcohol use during pregnancy and development of AD in offspring (pooled odds ratio [OR] 1.16; 95% confidence interval [CI] 1.09–1.24). However, there was no consistent association between AD in adults and adolescents and alcohol use (pooled OR 1.06; 95% CI 0.92–1.23). There is a need for future well-designed prospective studies to firmly establish the association between alcohol use and AD.

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Conflict of interest

Dr. Thyssen has attended advisory boards for Roche and Sanofi-Genzyme and received speaker honorarium from LEO Pharma. Dr. Egeberg has received research funding from Pfizer and Eli Lilly, and honoraria as consultant and/or speaker from Pfizer, Eli Lilly, Novartis, Galderma and Janssen Pharmaceuticals. Dr. Silverberg has received honoraria as an advisory board member or consultant from AbbVie, Eli Lilly, Galderma, GlaxoSmithKline, Kiniksa, Leo, Menlo, Pfizer, Regeneron-Sanofi, Realm, Roivant, and as a speaker for Regeneron-Sanofi. Ms. Halling-Overgaard, Mr. Holm and Drs. Hamann and Linneberg have no relevant interests to declare.

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Introduction

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease affecting 10–20% of children in industrialized countries.¹ AD is associated with skin barrier impairment and T helper (Th) 2 deviation of the immune system, caused by a

combination of genetic alterations and environmental insults.¹ As most cases of AD begin within the first 2 years of life,¹ the effects of certain gestational exposures on AD development risk have previously been studied.^{2–10} For example, there is some evidence that maternal stress, depression and anxiety during

pregnancy increase the risk of AD in offspring.^{2–7} Interestingly, high levels of plasma immunoglobulin E (IgE) during pregnancy and Th2 cell deviation in early life have been associated with AD development.^{11–13} Alcohol use stimulates Th2 cell deviation and increases plasma IgE levels,^{14–17} and could therefore at least in theory increase the risk of AD. However, the risk of maternal alcohol use during pregnancy on AD development risk in offspring is unclear.^{18–20}

In addition to the potential risk of AD associated with maternal alcohol use, studies have examined whether AD itself is associated with alcohol use or abuse. Notably, AD has been associated with other poor health behaviours including smoking and a sedentary lifestyle; however, these associations have mainly been investigated in cross-sectional studies.^{21,22} Moreover, adults with AD have an increased prevalence of psychiatric diseases including anxiety and depression, and report reduced quality of life possibly influencing alcohol use behaviours.^{23–25} Notably, alcohol use has also been investigated in other chronic inflammatory skin diseases including psoriasis and hidradenitis suppurativa.^{26–28} While psoriasis is associated with alcohol use,^{26,28} there are only limited data on the association between hidradenitis suppurativa and alcohol use.²⁷

In this systematic review and meta-analysis, the relationship between AD and alcohol use was investigated in two ways: (i) whether alcohol use during pregnancy is associated with AD in offspring and (ii) whether AD is associated with increased alcohol use.

Materials and methods

The aims of the systematic review and meta-analysis along with the search strategy and analysis plan were developed in Danish prior to study start, but no protocol was registered online on the systematic review protocol database PROSPERO. The medical databases PubMed, EMBASE and Web of Science were searched by AH and RPH during December 2016 using the following search term: '(atopic dermatitis OR atopic eczema OR children's eczema OR flexural dermatitis) AND (drinking OR alcohol OR alcoholic)'. The same two authors (AH and RPH) independently reviewed titles and abstracts of studies that examined the association between alcohol use and AD. Studies were also identified by screening reference lists of key articles and review articles. The search process is outlined in the PRISMA flow diagram (Fig. 1).

Studies were included in the systematic review and qualitative analysis *a priori*, if they investigated alcohol use in individuals or patients with AD and had a group with reference individuals, i.e. individuals without AD. Studies that listed the total number of patients with AD, the number of patients with AD and alcohol use, the total number of reference individuals and the number of reference individuals with alcohol use, or studies that listed the total number of pregnancy alcohol users, the number of pregnancy alcohol users with AD in offspring, the total number of

pregnancy non-alcohol users and the number of pregnancy non-alcohol users with AD in offspring, were included in the quantitative data analysis and hence the meta-analysis. Furthermore, primary data were reconstructed in studies that included summary measures for binary data, related confidence intervals (CI) and sample sizes.²⁹ Studies without primary epidemiological data or reconstructed primary epidemiological data on the association between AD and alcohol use or alcohol use during pregnancy and AD in offspring were only included in qualitative analysis. No limitation was set regarding the year of publication, language of the study or the age of study participants. Furthermore, no restriction was made regarding the definition of AD or the definition of alcohol use.

All authors of all articles included in the qualitative analysis were contacted, requesting primary epidemiological data on AD and alcohol use. If data were duplicated in more than one study, the study with most comprehensive data was included. After identification of the included studies, two authors (AH and RPH) independently performed data extraction. If studies that investigated alcohol use during pregnancy and AD in offspring had data on both alcohol use during early and late pregnancy, data from early pregnancy were used. Furthermore, if studies had data on developing AD in offspring at different ages, the oldest age of the children was used.

The quality of all studies included in the quantitative analysis was assessed using the Newcastle–Ottawa scale (NOS). The NOS is a point system used to assess the quality of non-randomized studies according to three primary items: selection, comparability and exposure (case–control studies) or outcome (cohort studies).³⁰ As the existing NOS is only applicable for cohort and case–control studies, an adapted version of NOS was used for cross-sectional studies. The adapted version for cross-sectional studies also used the point system to assess the quality of studies according to selection, comparability and outcome. A total of nine multiple choice questions were used in both the original and adapted NOS to assess the quality of the three primary items and a study could obtain a maximum of nine points according to the original NOS and 10 points according to the adapted NOS. Cohort and case–control studies with a NOS score of 6 or higher are considered to be of good quality, and we considered cross-sectional studies, assessed according to the adapted NOS, with an adapted NOS score of 7 or higher, to be of good quality.

Included studies were grouped in two categories: (i) one category for the association between alcohol use during pregnancy and AD in offspring and (ii) another category for the association between a diagnosis of AD and alcohol use. Subanalyses by study design, geographical region, study size, active vs. previous active AD and amount of alcohol use (light alcohol use vs. heavy alcohol use) were performed in the category for the association between AD and alcohol use.

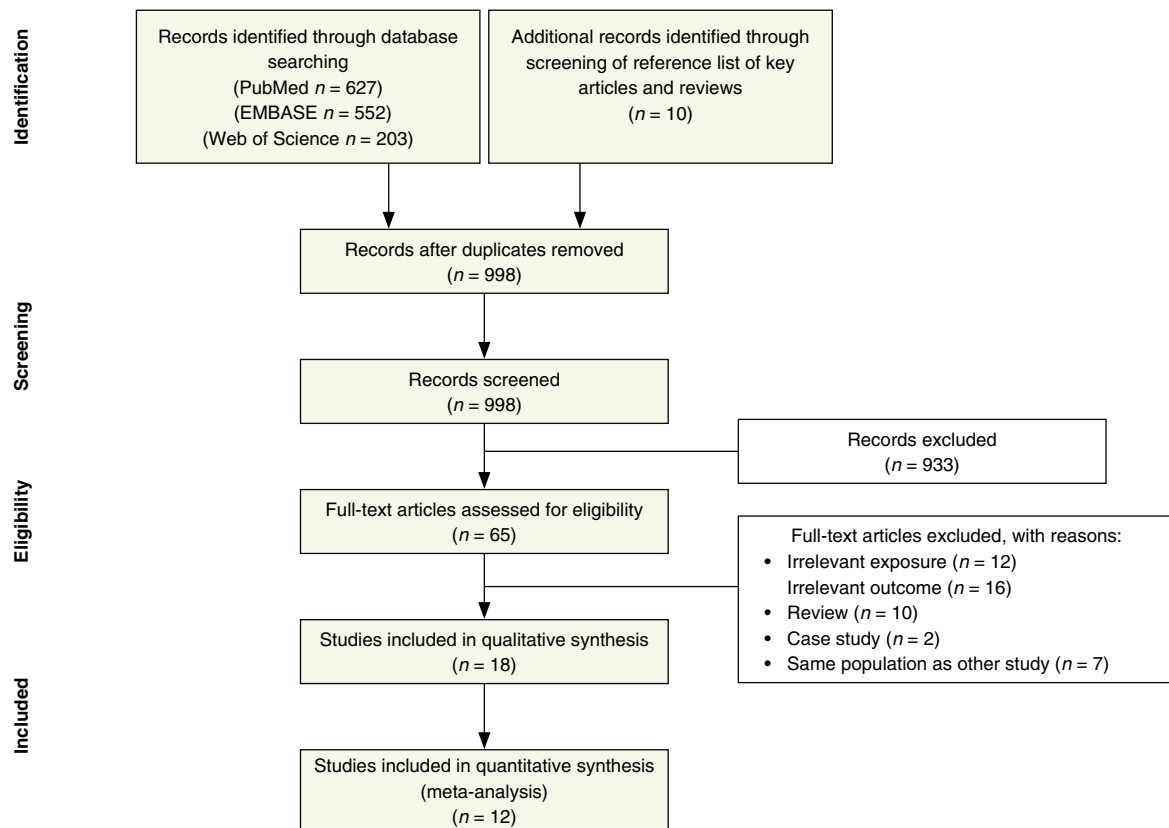


Figure 1 Flow diagram.

Statistical analysis

Odds ratios (OR) with 95% CI were calculated for all examined endpoints. The endpoints were as follows: (i) AD rates in offspring of mothers who used alcohol during pregnancy compared to mothers who did not use alcohol; and (ii) alcohol use in individuals with AD compared to reference individuals. The latest collection point was used to determine AD status in offspring. For example, we used data on AD before the age of 18 months instead of 3 months from a Danish cohort study.²⁰ For both endpoints, we assessed heterogeneity using Cochran Q and I^2 statistics, and constructed forest plots to visually display study results. We used random-effects models with DerSimonian-Laird methods, as there was significant between-study heterogeneity with Cochran Q statistics P -values <0.05 and $I^2 > 75\%$. We assessed publication bias using funnel plots. All statistical tests were two-sided, with a significance level of <0.05 . StatsDirect version 3 (StatsDirect Ltd., Cheshire, UK) was used for all statistical analyses.

Results

Overall, 1392 studies were identified in the screening process. After removing duplicates, 998 studies were identified of which 933 studies were excluded after title and abstract review. After full-text review, 47 studies were excluded due to irrelevant exposure ($n = 12$), irrelevant outcome ($n = 16$), study type; a review ($n = 10$) and a case study ($n = 2$), and due to the same population as other studies ($n = 7$). Eighteen studies were included in the review and qualitative analysis of which twelve studies were included in the quantitative analysis. In the first category, 'alcohol use during pregnancy and AD in offspring', a total of five studies were included (Tables S1 and S2).^{18–20,31,32} Of these, four studies were included in the quantitative analysis^{18–20,31} and one in the qualitative analysis.³² In the second category, 'AD and alcohol use', a total of thirteen studies were included (Tables S3 and S4).^{22,33–44} Of these, eight studies were included in the quantitative analysis^{22,33–38,40} and five studies in the qualitative analysis.^{39,41–44} All studies included in the quantitative analysis had a NOS score of 7 or higher, which is considered as a good score.

The four quantitatively analysed studies in the category 'alcohol use during pregnancy and AD in offspring' included 16 271 alcohol users during pregnancy and 29 811 non-alcohol users during pregnancy.^{18–20,31} Three of these studies were birth cohorts^{18–20} and one was cross-sectional.³¹ They originated from four different countries: Denmark ($n = 1$),²⁰ Japan ($n = 1$),¹⁸ United Kingdom ($n = 1$)¹⁹ and Germany ($n = 1$).³¹ There was a significant association between alcohol use during pregnancy and AD in offspring (pooled OR: 1.16; 95% CI: 1.09–1.24; P -value [P] < 0.0001; Fig. 2). However, all of the four studies included in the quantitative analysis reported mixed results.^{18–20,31} The large Danish cohort study found an association between alcohol use during pregnancy and AD at 2 months and at 18 months (example, 2–3" drinks per week in early pregnancy: unadjusted hazard ratio [HR] 1.46; unadjusted 95% CI: 1.10–1.94; adjusted HR 1.47; adjusted 95% CI: 1.10–1.95).²⁰ The German cross-sectional study found a positive association when adjusting for age and gender (OR: 1.19; 95% CI: 1.03–1.37), but no association in multivariate-adjusted analysis (OR: 1.03; 95% CI: 0.85–1.24). The Japanese cohort study found an increased risk of AD in children born to alcohol-using mothers at age 3 (unadjusted, $P = 0.15$; multivariate-adjusted, $P = 0.016$) and age 5 (unadjusted, $P = 0.079$; multivariate-adjusted, $P = 0.010$), but only in multivariate and not in unadjusted models. Notably, the United Kingdom cohort study found no association between maternal alcohol use during pregnancy and AD in offspring (example, ≥ 1 drinks per week in late pregnancy adjusted OR: 1.11; 0.93–1.33).¹⁹ Notably, two Danish studies, a cross-sectional study and a prospective cohort study, investigated the association between alcohol use during pregnancy among mothers with asthma and AD in offspring but these were not included as they used the same cohort as the included Danish cohort study.^{45,46} While the cross-sectional study found a non-significant

association between alcohol use during the third trimester of pregnancy and AD in offspring (adjusted OR: 1.88; 95% CI: 0.94–3.75),⁴⁶ the prospective cohort study showed a significant association (adjusted analysis, HR: 1.45; 95% CI: 1.04–2.02; $P = 0.029$).⁴⁵ In the qualitative analysis, one additional birth cohort from Singapore found no association between maternal alcohol use and AD in offspring ($n = 792$ participants, OR: 3.27; 95% CI: 0.39–27.53).³²

Three studies reported data on the amount of alcohol use.^{18–20} In the Japanese cohort, high compared to low alcohol use during pregnancy conferred an increased risk of AD in offspring.¹⁸ However, in two other cohort studies from Denmark and the United Kingdom, respectively, no dose-dependent association of alcohol use and AD development risk was found.^{19,20} Furthermore, the trimester in which alcohol was used did not affect the risk of AD in these two studies.^{19,20} The cohort from the United Kingdom found no overall association between maternal alcohol use and AD in offspring, but also found no difference in risk of alcohol use in early vs. late pregnancy. The cohort from Denmark found an association between alcohol use in both early pregnancy and late pregnancy and AD in offspring in adjusted models.^{19,20} The cohort from Japan found an association with alcohol use in the third trimester and AD in offspring.¹⁸ In addition to details on alcohol use, atopic history of parents was investigated in the cohort from Denmark. It was found that the risk of AD in offspring when using alcohol during pregnancy was primarily increased in children who had two parents with allergic disease.²⁰

The eight studies quantitatively analysed in the category 'AD and alcohol use' included 34 613 patients with AD and 246 397 reference individuals.^{22,33–38,40} Study designs included cross-sectional ($n = 6$),^{22,33–35,37,40} case-control ($n = 1$)³⁶ and cohort ($n = 1$).³⁸ They originated from four different countries: United States of America ($n = 3$),^{22,34,35} Korea ($n = 3$),^{33,37,40} Denmark ($n = 1$)³⁶ and Germany ($n = 1$).³⁸ All studies examined adults, except from one cohort study investigating AD patients with a median age of 15.2 years (reference individuals were age-matched)³⁸ and a cross-sectional study investigating adolescents (no further information regarding age was given).⁴⁰ Overall, there was no association between AD and alcohol use (pooled OR: 1.06; 95% CI: 0.92–1.23; $P = 0.44$; Fig. 3). The association remained non-significant irrespective of region (North America, Europe and Asia), study size (<5000 and >5000), amount of alcohol use (light alcohol use and heavy alcohol use) or whether the patients reported active AD vs. previous AD diagnosis (Table 1). However, both the association between AD and heavy alcohol use (pooled OR: 1.21; 95% CI: 0.92–1.60; $P = 0.078$) and the association between AD diagnosed during the last year and alcohol use (pooled OR: 1.09; 95% CI: 1.00–1.18; $P = 0.05$) appeared to be stronger than the overall association. Regarding the subanalyses on the study types, i.e. case-control, cohort and cross-sectional, no subanalyses were performed on case-control

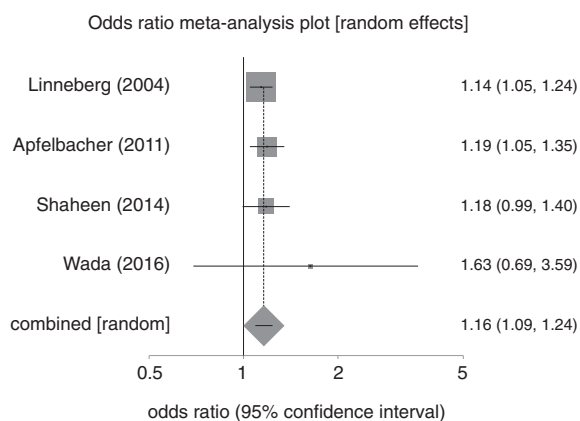


Figure 2 Forest plot of the association between maternal alcohol use during pregnancy and AD in offspring.

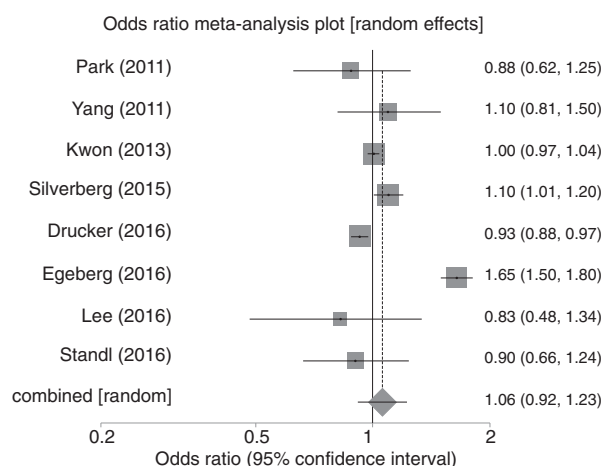


Figure 3 Forest plot of the association between AD and alcohol use in adults and adolescents.

Table 1 Odds ratio and 95% confidence interval for the association between AD and alcohol use in adults and adolescents based on meta-analysis of published literature

Study characteristics	OR (95% CI)
Overall	1.06 (0.92–1.23)
Study design	
Cross-sectional	0.99 (0.93–1.07)
Cohort	N/A*
Case-control	N/A†
Region	
Europe	1.24 (0.69–2.23)
North America	1.02 (0.88–1.18)
Asia	1.00 (0.97–1.04)
Study size	
<5000	0.96 (0.80–1.15)
>5000	1.10 (0.92–1.31)
Time when AD was diagnosed	
Diagnosed last year	1.09 (1.00–1.18)
Diagnosed in lifetime	1.05 (0.88–1.24)
Amount of alcohol use	
Light alcohol use	1.03 (0.81–1.32)
Heavy alcohol use	1.21 (0.92–1.60)

*Only one cohort study.

†Only one case-control study.

or cohort studies due to the low number of studies (case-control studies $n = 1$, cohort studies $n = 1$). However, a subanalysis on cross-sectional studies was performed (cross-sectional studies $n = 6$), but the association remained non-significant (pooled OR: 0.99; 95% CI: 0.93–1.07).

In addition to the quantitative analysis, five other cross-sectional studies were included in the qualitative analysis

encompassing 155 053 subjects (range 1976–75 643 subjects).^{39,41–44} These originated from Norway ($n = 1$),³⁹ Australia ($n = 1$)⁴¹ and Korea ($n = 3$)^{42–44} and investigated adolescents ($n = 2$)^{43,44} or adults ($n = 3$).^{39,41,42} AD was associated with current alcohol use in one study from Korea that investigated adolescents (OR: 1.18; $P < 0.05$).⁴⁴ However, none of the other two Korean studies found such a relationship ($[P = 0.006]$,⁴¹ [OR: 1.05; 95% CI: 1.00–1.11]⁴²). Moreover, no association between AD and alcohol was reported in the Norwegian study (women: adjusted OR: 0.64; 95% CI: 0.38–1.09, men: adjusted OR: 0.64; 95% CI: 0.38–1.09)³⁹ or in the Australian study ($P = 0.34$) where the mean alcohol intake of AD patients (5.6 g/day) was compared with that of reference individuals (6.7 g/day).⁴¹

Discussion

Main findings

In this systematic review and meta-analysis, there was a positive association between alcohol use during pregnancy and AD development in offspring. However, no consistent association was observed between AD and alcohol use in adolescents and adults.

Interpretation

Most proposed mechanisms of the association between alcohol use during pregnancy and AD development in offspring revolve around the inflammatory-modulating properties of alcohol. Animal studies have shown an association between alcohol use and Th2 deviation, and in human studies, plasma IgE levels increase after alcohol use.^{16,17} AD patients have a Th2-dominated inflammatory response and many also increased IgE response to allergens.¹ Normal pregnancy is also associated with Th2 cell deviation which persists for some months in the neonates until the Th1/Th2 ratio balances.^{47,48} Exposure to allergens, environmental insults and ostensibly alcohol use during pregnancy may further skew the Th2 deviation thereby increasing the risk of AD development.⁴⁸ Furthermore, studies have reported that both maternal high IgE levels and Th2 deviation are associated with AD in offspring.^{11–13} Notably, a study investigating 1,631 infants found a positive dose-response relationship between maternal alcohol use during pregnancy and IgE levels in the umbilical cord blood.⁴⁹

Importantly, it is well known that the relationship between alcohol use and various outcomes tends to be J- or U-shaped.⁵⁰ However, only three of the four included studies made a distinction between a light and heavy alcohol use and the definitions varied in-between studies.^{18–20} Hence, no quantitative analysis comparing a maternal light alcohol use with a maternal heavy alcohol use during pregnancy and the risk of AD in offspring was performed. The cohort from Denmark found an association between more than two alcoholic drinks per week during late pregnancy and AD in offspring (adjusted HR: 1.33; 95% CI: 1.02–1.73), while there was no association between 0.5 alcoholic

drinks per week during late pregnancy and AD in offspring (adjusted HR: 0.91; 95% CI: 0.69–1.22).²⁰ In addition, the cohort from Japan showed that the risk of AD in offspring tended to increase when mothers had high alcohol use compared to low alcohol use during pregnancy ($P = 0.002$).¹⁸ However, the cohort from United Kingdom found no association between AD in offspring and, respectively, <1 alcoholic drinks per week during the first 3 months of pregnancy (adjusted OR: 0.98; 95% CI: 0.86–1.13) and ≥ 1 alcoholic drinks per week during the first 3 months of pregnancy (adjusted OR: 1.08, 95% CI: 0.90–1.31).¹⁹

Atopic dermatitis in adults has been associated with several systemic comorbidities including asthma, allergic rhinitis, autoimmune and neuropsychiatric diseases.²⁴ Similarly, patients with AD report a diminished quality of life,⁵¹ and in recent years, AD status has been associated with some poor health behaviours.^{21,22} Given the positive association between AD and smoking,²¹ it seems reasonable that AD could be associated with increased alcohol use as well. Nonetheless, in this meta-analysis and review, we found no such relationship.

However, there were much fewer studies available of the relationship between AD and alcohol use than for smoking. Notably, studies have also investigated the association between other chronic inflammatory skin diseases and alcohol use. While there were limited data on the association between hidradenitis suppurativa and alcohol use,²⁷ there was an association between psoriasis and alcohol use.^{26,28,36} According to a Danish case-control study, the prevalence of alcohol abuse was higher among AD patients (7.1%) when compared with the general population (4.4%; adjusted OR: 1.38; 95% CI: 1.24–1.53, $P < 0.0001$), whereas the prevalence was lower among AD patients (7.1%) when compared to psoriasis patients (12.5%; adjusted OR: 0.57; 95% CI: 0.52–0.63, $P < 0.0001$).³⁶

Light alcohol use is commonplace in the Western and Asian countries where the studies included in this analysis originated from. Therefore, it seemed most likely that AD would be associated with a heavy alcohol use, rather than any alcohol use. However, in our subanalysis limited to heavy alcohol use, there was still no association found (OR: 1.21; 95% CI: 0.92–1.60). In addition to the amount of alcohol use, the severity of AD could be important worsening severity of AD correlated with worsened quality of life, which could ostensibly drive alcohol use.⁵² Only one of the included studies differentiated between mild and severe AD and found that patients with severe disease did indeed have a higher risk of alcohol abuse than mild AD patients.³⁶ Moreover, most of the included studies were general population studies, and it is reasonable to assume that more participants in the general population studies had mild or moderate AD rather than severe AD. Importantly, cross-sectional studies cannot determine the temporal association, and hence cause and effect. A potential association between AD and alcohol use could therefore be reversed, i.e. alcohol use results in a diagnosis of AD

rather than AD patients have increased alcohol use due to their disease. There is a need for future well-designed prospective studies investigating this possible association between AD and alcohol use, especially the association between severe AD and alcohol abuse.

Limitations

Only four studies were analysed in the category ‘alcohol use during pregnancy and AD in offspring’ and eight studies in the category ‘AD and alcohol use’. The definition of AD was based on questionnaires in all studies except one Danish cohort study where AD was defined as a hospital diagnosis of AD. Some degree of misclassification is therefore a concern. Moreover, information on AD severity and AD comorbidities were lacking, limiting any subanalysis on the role of AD severity or AD comorbidities on alcohol use.

Conclusion

This meta-analysis showed a positive association between maternal alcohol use during pregnancy and AD in offspring, whereas no consistent association was observed between AD among adolescents and adults and alcohol use. There is a need for future well-designed prospective studies with quantitative assessment of alcohol use to firmly establish whether prenatal alcohol exposure increases the risk of AD in offspring. Furthermore, future studies need to address if adults with AD have an increased risk of alcohol abuse compared to the general population.

Author contributions

Thyssen, Egeberg and Halling-Overgaard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Thyssen and Halling-Overgaard designed and conceived the study. All authors acquired, analysed and interpreted the data. Thyssen, Halling-Overgaard and Hamann drafted the manuscript. All authors made a critical review of the manuscript for important intellectual content. Egeberg involved in statistical analysis. None involved in the funding of the manuscript. All authors involved in administrative, technical and material support. All authors supervised the study.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Studies containing information on alcohol use during pregnancy and risk of atopic dermatitis in offspring.

Table S2. Studies examining the association between alcohol use during pregnancy and atopic dermatitis in offspring– articles only included in the systemic review.

Table S3. Studies containing information on atopic dermatitis and alcohol use.

Table S4. Studies examining the association between atopic dermatitis and alcohol use – articles only included in the systemic review.

Supplementary Tables

Supplementary Table 1. Studies containing information on alcohol use during pregnancy and risk of atopic dermatitis in offspring.

Reference	Country	Study design	Assessment of AD	Assessment of alcohol use	<i>n total</i>	<i>n pregnancy alcohol users total</i>	<i>n pregnancy alcohol users with AD child</i>	<i>n pregnancy non-alcohol users, total</i>	<i>n pregnancy non-alcohol users with AD child</i>
Linneberg et al (2004) ¹	Denmark	Prospective birth cohort	AD before 18 months defined as a child whose mother reported that the child had or had had (1) an itchy rash and/or doctor verified AD, and (2) recurrent rash and/or rash for at least 4 consecutive half month periods, and (3) localization of the rash in elbow creases, behind the knees, face, wrists/hands, or generalized. They also investigated AD before 2 months at life.	Alcohol use defined as $\geq \frac{1}{2}$ drinks/week (1 drink contains 12 g of alcohol) during late pregnancy. There was data on alcohol use respectively $\frac{1}{2}$, 1-1½, 2-3½ and ≥ 4 drinks. We used data on late pregnancy, but there was data on both early and late pregnancy.	Early pregnancy: 24,290 Late pregnancy: 24,193	Early pregnancy: 11,236 Late pregnancy: 12,642	Early pregnancy: 1,218 Late pregnancy: 1,435	Early pregnancy: 13,054 Late pregnancy: 11,551	Early pregnancy: 1,397 Late pregnancy: 1,167
Apfelbacher et al (2010) ²	Germany	Cross-sectional	Eczema defined as an affirmative response to the question “Has a physician ever diagnosed eczema (atopic dermatitis or endogenous eczema)?”	Maternal alcohol use during pregnancy.	16,761	2,242	341	14,519	1,902
Shaheen et al (2014) ³	United Kingdom	Prospective birth cohort	Childhood eczema defined as an affirmative response to having eczema (the question asked was “Has your child had any of the following in the past 12 months: wheezing, asthma, eczema, hay fever?”).	Alcohol use defined as ≥ 1 alcohol units per week during the last 2 months of pregnancy (late pregnancy). We used data on late pregnancy, but there was also data on alcohol use during 8 weeks at pregnancy and during the first three months of pregnancy (early pregnancy).	Early pregnancy: 4,560 Late pregnancy: 4,782	Early pregnancy: 1,174 Late pregnancy: 1,346	Early pregnancy: 211 Late pregnancy: 232	Early pregnancy: 3,379 Late pregnancy: 3,436	Early pregnancy: 579 Late pregnancy: 515
Wada et al	Japan	Prospective	AD before the age of 5 years	Alcohol use defined as	346	41	11	305	56

(2016) ⁴		birth cohort	defined as an affirmative response to the question “Has a doctor ever said that your child had atopic eczema?” and through ISAAC questions. They also investigated AD before the age of 3 years.	any alcohol use derived from alcoholic beverages in the third trimester of pregnancy.					
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AD: atopic dermatitis, ISAAC: International Study of Asthma and Allergies in Childhood.

Supplementary Table 2. Studies examining the association between alcohol use during pregnancy and atopic dermatitis in offspring—articles only included in the systemic review

Reference	Country	<i>n</i> <i>total</i>	Study design	Assessment of AD	Assessment of alcohol use	Qualitative results
Loo et al (2015) ⁵	Singapore	792	Prospective birth cohort	AD defined as an affirmative response to the question “Has your child ever been diagnosed with eczema?”	Maternal alcohol use. There was no information whether alcohol use was during pregnancy.	There was no association between maternal alcohol use during pregnancy and AD in offspring (a multivariate analysis, OR 3.27; 95% CI 0.39-27.53; p=0.28).

AD: atopic dermatitis, OR: odds ratio, 95% CI: confidence interval, p: p-value.

Supplementary Table 3. Studies containing information on atopic dermatitis and alcohol use

Reference	Country	Participant age (Years)	Sex (Female/Male)	Study design	Assessment of AD	Assessment of alcohol use	<i>n</i> total	<i>n</i> AD patients total	<i>n</i> AD patients with a alcohol use	<i>n</i> reference individuals total	<i>N</i> reference individuals with a alcohol use
Park et al (2011) ⁶	Korea	Adults ≥ 20	AD patients: 120/97 Reference individuals: 875/898	Cross-sectional	Lifetime AD and AD diagnosed during the last year, both defined as self-reported history of doctor diagnosed AD.	Occasionally alcohol use defined as alcohol use less than once per month. Frequent alcohol use defined as alcohol use more than once per month. We compared no alcohol use with respectively, a	Any alcohol use: <i>Lifetime AD:</i> 1,942 <i>AD diagnosed during the last year:</i>	Any alcohol use: <i>Lifetime AD:</i> 214 <i>AD diagnosed during the last year:</i> 173	Any alcohol use: <i>Lifetime AD:</i> 162 <i>AD diagnosed during the last year:</i> 132	Any alcohol use: <i>Lifetime AD:</i> 1,728 <i>AD diagnosed during the last year:</i> 1,769	Any alcohol use: <i>Lifetime AD:</i> 1,348 <i>AD diagnosed during the last year:</i> 1,378

						combination of occasionally and frequent alcohol use (any alcohol use) and occasionally alcohol use (light alcohol use).	1,942 Light alcohol use: <i>Lifetime AD: 905</i> <i>AD diagnosed during the last year: 905</i>	Light alcohol use: <i>Lifetime AD: 101</i> <i>AD diagnosed during the last year: 80</i>	Light alcohol use: <i>Lifetime AD: 49</i> <i>AD diagnosed during the last year: 39</i>	Light alcohol use: <i>Lifetime AD: 804</i> <i>AD diagnosed during the last year: 825</i>	Light alcohol use: <i>Lifetime AD: 424</i> <i>AD diagnosed during the last year: 434</i>
Yang et al (2011) ⁷	United States of America	AD patients, mean (SD): 38.4 (11.8) Reference individuals, mean (SD): 37.6 (11.2)	AD patients: 170/117 Reference individuals: 1,327/1,360	Cross-sectional	Lifetime eczema defined as an affirmative response to the question "Have you ever had an itchy skin rash which was coming and going for at least 6 months?" and "Had this skin 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?" or an affirmative response to "Has a doctor or other health professional ever told you that you have eczema?"	Alcohol use defined as ≥ 12 drinks/year (any alcohol use).	Any alcohol use: 2,974	Any alcohol use: 287	Any alcohol use: 225	Any alcohol use: 2,687	Any alcohol use: 2,064
Kwon et	Korea	Adolescents	27,230/28,5	Cross-	AD defined as an	Alcohol use defined	73,238	15,892	Any	57,346	Any

al (2013) ⁸		, no further information was given	01	sectional	affirmative response to the question “In your life, have you ever been diagnosed with atopic dermatitis by a doctor?”	as more than one glass of alcohol per day per month (any alcohol use).			alcohol use: 8,772		alcohol use: 31,586
Drucker et al (2016) ⁹	United States of America	AD patients, mean (SD): 54.5 (4.6) Reference individuals, mean (SD): 54.5 (4.6)	Only females	Cross-sectional	AD defined as an affirmative response to the question “Ever had clinician-diagnosed eczema (atopic dermatitis)”.	Alcohol use defined as g/day and categorized in groups according to the amount of g/day. We compared 0 g/day with respectively 1-≥30 g/day (any alcohol use), 1-4 g/day (light alcohol use) and ≥ 30 g/day (heavy alcohol use).	Any alcohol use: 72,759 Light alcohol use: 47,151 Heavy alcohol use: 27,543	Any alcohol use: 7,356 Light alcohol use: 4,833 Heavy alcohol use: 2,924	Any alcohol use: 4,750 Light alcohol use: 2,227 Heavy alcohol use: 318	Any alcohol use: 65,403 Light alcohol use: 42,318 Heavy alcohol use: 24,619	Any alcohol use: 43,372 Light alcohol use: 20,287 Heavy alcohol use: 2,588
Egeberg et al (2016) ¹⁰	Denmark	Adults ≥ 18 AD patients, mean (SD): 34.4 (14.1) Reference individuals, mean (SD): 34.3 (14.1)	AD patients: 4,901/3,036 Reference individuals: 49,010/30,360	Case-control	AD defined as an inpatient or outpatient hospital diagnosis of AD (ICD 10 L20).	Alcohol abuse defined as an alcohol abuse diagnosis, a condition strongly related to alcohol abuse or a treatment used for alcohol dependence (heavy alcohol use).	Heavy alcohol use: 87,307	Heavy alcohol use: 7,937	Heavy alcohol use: 563	Heavy alcohol use: 79,370	Heavy alcohol use: 3,520
Lee et al (2016) ¹¹	Korea	19-40	AD patients: 132/98 Reference individuals: 2,830/2,152	Cross-sectional	AD defined as an affirmative response to the question “Have you ever been diagnosed as having AD by a physician?”	Heavy alcohol use defined as drinking ≥ 30g/day (heavy alcohol use).	Heavy alcohol use: 5,212	Heavy alcohol use: 230	Heavy alcohol use: 19	Heavy alcohol use: 4,982	Heavy alcohol use: 490
Silverberg et al (2015) ¹²	United States of America	18-85	Not given	Cross-sectional	Eczema defined as an affirmative response to the question “During the past 12	Alcohol use defined as ≥ 12 drinks of alcoholic beverage in 1 year (any alcohol use).	Any alcohol use: 34,588	Any alcohol use: 2,488 Light	Any alcohol use: 1,647 Light	Any alcohol use: 32,100 Light	Any alcohol use: 20,576

					months, have you been told by a doctor or other health professional that (child) had eczema or any kind of skin allergy?" No specific definition of AD.	We also compared lifetime abstainer (<12 drinks in lifetime) with respectively, current light alcohol use (12+ drinks in lifetime and <3 drinks per week in past year) (light alcohol use) and current heavy alcohol use (>12 drinks in lifetime and (male) >14 drinks per week in the past year or (female) >7 drinks per week in the past year) (heavy alcohol use).	Light alcohol use: 18,027 Heavy alcohol use: 9,002	alcohol use: 1,207 Heavy alcohol use: 560	alcohol use: 794 Heavy alcohol use: 147	alcohol use: 16,820 Heavy alcohol use: 8,442	Light alcohol use: 9,951 Heavy alcohol use: 1,573
Standl et al (2016) ¹³	Germany	AD patients, median (25th-75th percentile): 15.2 (15.1-15.3) Reference individuals, median (25th-75th percentile): 15.2 (15.1-15.3)	AD patients: 413/401 Reference individuals: 751/721	Cohort	AD defined as self-reported doctor diagnosis of AD.	Alcohol use defined as g/day and categorized in groups according to the amount of g/day. We compared no alcohol use with respectively ≥ 0 - >80 g/day (any alcohol use), ≥ 0 - <20 g/day (light alcohol use) and ≥ 40 - >80 g/day (heavy alcohol use).	Any alcohol use: 2,990 Light alcohol use: 2,119 Heavy alcohol use: 1,231	Any alcohol use: 209 Light alcohol use: 157 Heavy alcohol use: 90	Any alcohol use: 142 Light alcohol use: 90 Heavy alcohol use: 23	Any alcohol use: 2,781 Light alcohol use: 1,962 Heavy alcohol use: 1,141	Any alcohol use: 1,951 Light alcohol use: 1,132 Heavy alcohol use: 311

AD: atopic dermatitis, SD: standard deviation, ICD: International Classification of Diseases.

Supplementary Table 4. Studies examining the association between atopic dermatitis and alcohol use – articles only included in the systemic review

Referen	Country	n total	Age (years)	Sex	Study	Assessment of AD	Assessment of	Qualitative results
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ce				(Female/male)	design		alcohol use	
Bø et al (2008) ¹⁴	Norway	18,747 AD patients: 1,184 Reference individuals: 17,563	Born in 1970, 1960, 1955, 1940-1941 or 1924-1925.	10,355/8,392	Cross-sectional	AD defined as an affirmative response to the question "Did the doctor tell you that you have had (yes/no) either acne, psoriasis, atopic dermatitis, hand eczema, skin cancer or any other skin disease?"	Alcohol units per week or month.	Alcohol use 4-7 times a week was not associated with AD among women (adjusted OR 0.64; 95% CI 0.38-1.09) or men (adjusted OR 1.11; 95% CI 0.59-2.12).
Sanna et al (2014) ¹⁵	Australia	2,027 AD patients: 782 Reference individuals: 1,299	AD patients, median (range): 51.2 (35.7-64.3) Reference individuals, median (range): 58.5 (43.1-72.5)	AD patients: 512/270 Reference individuals: 573/672	Cross-sectional	Self-reported eczema. No specific definition of AD was given.	Mean alcohol use defined as g/day.	AD patients and reference individuals mean alcohol use was respectively 5.6 g/day and 6.7 g/day (p=0.343).
Kim et al (2015) ¹⁶	Korea	1,976 AD patients: 103 Reference individuals: 1,873	19-39	0/1,976	Cross-sectional	Not given.	Current alcohol users defined as >30 g/day.	A lower percentage of AD patients were current alcohol users when compared to reference individuals (p=0.006).
Lee et al (2016) ¹⁷	Korea	75,643 AD patients: 17,474 Reference individuals: 58,169	13-18	Not given	Cross-sectional	AD defined as an affirmative response to the question "Have you ever been diagnosed with atopic dermatitis (or eczema) by a doctor?"	Alcohol use defined as using alcohol more than once per month.	AD was not associated with alcohol use (OR 1.05; 95% CI 1.00-1.11).
Rha et al (2016) ¹⁸	Korea	74,167	Adolescents, no further information was given	Not given	Cross-sectional	Not given.	Current alcohol use.	Current alcohol use was associated with AD (OR 1.18; p<0.05).

AD: atopic dermatitis, OR: odds ratio, 95% CI: confidence interval, p: p-value.

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