

Alcohol during pregnancy and atopic dermatitis in the offspring

A. Linneberg*, J. Petersen*, M. Grønæk† and C. S. Benn‡

*Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark, †Centre for Alcohol Research, National Institute of Public Health, Copenhagen, Denmark, ‡Danish Epidemiology Science Centre, Statens Serum Institut, Copenhagen, Denmark

Summary

Background There is evidence that antenatal factors play a role in the development of atopic dermatitis (AD). However, little is known about the effects of maternal lifestyle factors during pregnancy on the risk of AD in the offspring.

Objective To investigate the effect of alcohol consumption during pregnancy on the incidence of AD in the offspring.

Methods A total of 24 341 mother–child pairs enrolled in the Danish National Birth Cohort were followed prospectively. Information about alcohol consumption was obtained by interview at 12 and 30 weeks of gestation. Information about symptoms, time of onset, and doctor's diagnosis of AD in the offspring was obtained by interview at 18 months of age. The effect of alcohol consumption during pregnancy on the incidence of AD was analysed by Cox regression allowing for different effects of alcohol before (early infancy) and after 2 months (60 days) of age.

Results Alcohol during pregnancy was associated with a significant and dose-dependent increased risk of AD in early infancy. This effect was mainly seen in high-risk infants (two parents with allergic disease). Thus, the highest risk of AD in early infancy was seen in high-risk infants of mothers who consumed four or more drinks per week at 30 weeks of gestation (adjusted relative risk 4.2, 95% confidence interval 1.7–10.1). There was no effect of alcohol during pregnancy beyond early infancy.

Conclusions The results suggest that alcohol during pregnancy increases the risk of early-onset AD in predisposed infants.

Key words alcohol drinking, alcoholic beverages, atopic dermatitis, pregnancy

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The prevalence of atopic dermatitis (AD) has increased in westernized countries, and AD is considered a public health problem world-wide [1]. The causes of this increase are largely unknown. In Denmark, the cumulated incidence of AD in 7-year-old children born in 1960–1964 was relatively low, i.e. 3.2%. Subsequently, the incidence of AD has been steadily increasing in successive birth cohorts, and in 1987 the cumulated incidence of AD in 7-year-old children born in 1975–1979 was 11.5% [2]. Thus, it is likely that changes in lifestyle and environmental factors that occurred around 1960 are responsible for the increase in AD. The parallel increase in the prevalence of IgE sensitization against inhalant allergens observed in Danish adults also appears to have started with generations born around 1960 [3]. Many changes occurred at that time and it is a difficult task to disentangle the individual effect of each factor. However, consumption of alcoholic drinks is one factor that changed dramatically around 1960. In the total population of Denmark, the annual consumption of alcohol per inhabitant more than doubled from 1955 to 1973 (from approximately 4.5 to 11 L pure alcohol) [4]. This

trend is in line with trends of alcohol consumption in the UK (http://www.acmedsci.ac.uk/p_callingtime.pdf). Moreover, alcohol consumption during pregnancy is frequent in westernized countries [5–8].

There is evidence that factors that operate *in utero* or in early life play a role in the development of atopic disease [9–11]; this is particularly evident for AD that often develops during the first months of life as the first manifestation of atopic disease. In a German birth cohort study, early-onset AD was frequent (the period prevalence of AD in the first 3 months of life was 4.8%), and predicted allergic airway disease at 5 years [12]. Recent findings suggest that factors, which influence cytokine production by the fetoplacental unit, may be important determinants of atopic disease [13]. Nevertheless, there is limited data on the effects of maternal lifestyle factors during pregnancy.

In a large national birth cohort, we aimed to investigate the effect of alcohol consumption during pregnancy on the incidence of AD in the offspring.

Materials and methods

Participants

The study was based on mother–child pairs enrolled in The Danish National Birth Cohort (DNBC) [14]. Women were

Correspondence: Allan Linneberg, Research Centre for Prevention and Health, Glostrup University Hospital, 57 Nrd Ringvej, Building 84/85, DK-2600 Glostrup, Denmark.

E-mail: alli@glostruphosp.kbhamt.dk

invited to participate when they came to their general practitioner for the first pregnancy consultation. Participation involved four computer-assisted telephone interviews at gestational weeks 12 and 30 (first and second interview) and when the child was 6 and 18 months old (third and fourth interview). The DNBC has consecutively recruited 100 000 pregnant women from 1997 to 2002. April 2000, the fourth interview was modified and hereafter included questions about AD. The women were called up to four times for each interview. If not found at home and available for interview, the interview was cancelled. Almost no women actively denied participation. When the present study was initiated in 2002, 44 779 women were due to have taken part in the modified fourth interview. However, 20 438 missed one or more of the interviews. We enrolled the 24 341 remaining pairs. The DNBC was approved by The Ethical Committees in Denmark and by the Data Protection Board.

Measurement of exposure

Information about alcohol consumption during pregnancy was obtained at 12 (first interview) and 30 (second interview) weeks of gestation. In these interviews, the participants were asked to report their current average weekly intake of beer, wine, and spirits. The question was 'How many beers do you drink per week' and the same question was asked for 'glasses of wine' and 'glasses of spirits'. In the first interview, they were also asked about alcohol consumption before their pregnancy. Women who reported an alcohol intake of less than one drink per week were given a separate code, which was assigned a numeric value of 0.5 drink. One bottle of beer contains 12 grams of alcohol, which is the approximate average for one serving (1/6 bottle) of wine or one drink (4 CL) of spirits in Denmark. The total weekly alcohol consumption was calculated by adding the intake of beer, wine, and spirits.

Measurement of outcome

A diagnosis of AD was based on data obtained in the fourth interview when the child was 18 months of age. The mother was asked whether the child had ever had an itchy rash, and if so, about localization and age when affected (recorded as half-month periods). She was also asked whether the child had AD, and if so whether a doctor had verified the diagnosis. As described elsewhere, a dermatologist examined a subgroup of the participating infants and the combination of answers that resulted in the highest sum of sensitivity and specificity was determined [15]. Thus, cases of AD were defined as children whose mothers 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 (four or more localizations). The time of onset was calculated as the middle day in the first half-month period that the mother reported symptoms, i.e. the age of onset was 7, 22, 38, etc., or 548 days.

Measurement of confounders

Data on birth characteristics (birth weight, head circumference, and gestational age) was obtained from The Danish Medical Birth Registry. Data on other variables were obtained from the interviews.

Statistical analysis

The effect of alcohol consumption during pregnancy on AD was studied in Cox regression (proportional hazards) models [16] with age as the underlying time.

It was hypothesized that a possible effect of alcohol on the immune system during gestation would tend to attenuate after birth. Therefore, alcohol consumption was modelled as a time-dependent coefficient where alcohol was allowed to have one effect on AD during the first 60 days of the child's life (early infancy) and another effect after the first 60 days (late infancy).

The three alcohol variables (alcohol before pregnancy, alcohol at 12 and 30 weeks of gestation) were analysed in separate models. The following confounders were considered: maternal age (<25, 25–29, 30–34, ≥35 years), sex, parental allergic disease (none, one parent, both parents with a history of hayfever, asthma, or AD), breastfeeding at 6 months (yes, no), number of siblings (modelled as a linear trend), occupational class (high, medium, low, unemployed, other), maternal vocational training (yes/no), maternal smoking during pregnancy at 30 weeks of gestation (yes/no), maternal smoking at 6 months postnatally (yes/no), household income (high, low, unknown), pets in the home (yes/no), day care at 6 months (yes/no), season of birth (spring, summer, autumn, winter), birth weight (<2500, 2500–3000, 3000–3500, 3500–4000, ≥4000 g, unknown), head circumference (<34, 34–37, ≥37, unknown), and gestational age (<37, 37–42, ≥42 weeks).

The proportional hazard assumption was checked by investigating plots of the integrated hazard functions and plots of the Schoenfeld's residuals. In the adjusted analyses, 'parental allergic disease' was included as a strata variable, since this variable did not meet the criteria for proportional hazards. In order to investigate interaction between the effect of alcohol and atopic predisposition, separate analyses were performed for each level of 'parental allergic disease'. All analyses were performed with SAS version 8.2.

Results

High socio-economic level (household income and educational level of the mother) appeared to be positively associated with alcohol consumption before and during pregnancy (Table 1). Parental allergic disease was not associated with alcohol consumption.

Table 2 shows that alcohol consumption during pregnancy (both at 12 and 30 weeks of gestation) was significantly associated with an increased risk of developing AD during the first 2 months of life (early infancy), but not beyond this period (late infancy). There was a non-significant negative association between maternal smoking during pregnancy and the incidence of AD (data not shown).

Table 1. The prevalence (%) of different variables by alcohol consumption before pregnancy and during pregnancy at 12 (early pregnancy) and 30 (late pregnancy) weeks of gestation

Alcohol consumption (drinks/week)	N	AD before 2 months	AD before 18 months	Age ≥ 35 years	BF	BW ≥ 3500 g	HC ≥ 37 cm	Atopic parent ≥ 1	Smoking 12 weeks*	Smoking 30 weeks*	Pets in home	Medium or High education	High income
Before pregnancy													
Non-drinkers	2860	1.96	9.5	11.8	56.0	56.4	21.5	53.0	32.1	26.2	50.2	22.1	34.9
$\frac{1}{2}$	2528	2.02	10.1	12.7	60.5	59.7	24.2	52.9	24.9	18.5	47.9	31.3	38.9
1–1 $\frac{1}{2}$	5651	1.82	10.6	12.4	63.2	60.5	22.9	53.3	23.2	16.9	44.7	35.9	43.1
2–3 $\frac{1}{2}$	5993	2.02	11.2	15.2	67.6	60.9	24.1	53.3	21.1	14.4	41.0	42.9	51.3
≥ 4	7191	2.02	11.3	20.3	68.6	59.8	22.6	52.7	27.6	17.7	37.1	46.7	56.3
Early pregnancy													
Non-drinkers	13054	1.70	10.7	12.8	63.1	59.8	23.1	53.9	25.1	17.7	43.4	35.8	43.9
$\frac{1}{2}$	3909	2.20	10.7	14.8	65.8	60.1	22.9	52.3	23.7	16.2	41.1	39.5	47.7
1–1 $\frac{1}{2}$	4397	2.27	10.5	17.1	67.8	60.3	23.6	52.7	24.1	16.1	41.1	43.8	52.4
2–3 $\frac{1}{2}$	2425	2.47	11.5	22.9	66.6	59.7	22.7	50.8	28.0	20.9	41.0	43.8	57.4
≥ 4	505	1.78	11.7	37.0	63.8	55.1	21.4	51.3	39.2	33.9	48.3	39.2	56.2
Late pregnancy													
Non-drinkers	11551	1.74	10.1	12.3	60.9	59.3	23.1	53.1	27.7	20.5	45.2	31.9	41.0
$\frac{1}{2}$	3611	1.66	10.7	14.4	68.0	59.2	22.7	54.3	20.2	12.8	38.5	43.2	49.1
1–1 $\frac{1}{2}$	4917	2.28	12.0	16.3	69.4	61.6	23.4	53.5	22.6	14.7	40.5	44.5	52.2
2–3 $\frac{1}{2}$	3253	2.40	11.2	22.1	68.5	61.3	23.6	52.0	23.9	16.8	39.7	47.4	59.5
≥ 4	861	2.67	11.0	32.3	63.9	59.0	22.5	48.8	33.6	27.3	44.1	45.8	59.0

*Maternal smoking at 12 or 30 weeks of gestation (at first or second interview).

AD, atopic dermatitis; BW, birth weight; BF, breastfeeding at 6 months of age; HC, head circumference at birth.

Table 2. The relationship of alcohol consumption before pregnancy or during pregnancy at 12 (early pregnancy) or 30 (late pregnancy) weeks of gestation to the incidence of AD during the first 60 days of life and during 2–18 months of life

Alcohol consumption (drinks/week)	The effect of alcohol on AD at 0–2 months of life		The effect of alcohol on AD at 2–18 months of life	
	Crude HR*	Adjusted HR†	Crude HR*	Adjusted HR†
Before pregnancy				
Non-drinkers	1 (reference)	1 (reference)	1 (reference)	1 (reference)
$\frac{1}{2}$	1.03 (0.71–1.51)	1.00 (0.68–1.46)	1.07 (0.89–1.30)	1.04 (0.86–1.26)
1–1 $\frac{1}{2}$	0.93 (0.67–1.29)	0.88 (0.64–1.22)	1.17 (1.00–1.38)	1.12 (0.95–1.31)
2–3 $\frac{1}{2}$	1.03 (0.75–1.42)	0.96 (0.70–1.31)	1.22 (1.04–1.43)	1.14 (0.97–1.33)
≥ 4	1.03 (0.76–1.40)	0.95 (0.70–1.30)	1.25 (1.07–1.45)	1.15 (0.98–1.35)
Early pregnancy				
Non-drinkers	1 (reference)	1 (reference)	1 (reference)	1 (reference)
$\frac{1}{2}$	1.30 (1.01–1.66)	1.29 (1.00–1.65)	0.95 (0.84–1.07)	0.94 (0.83–1.06)
1–1 $\frac{1}{2}$	1.34 (1.06–1.70)	1.31 (1.03–1.66)	0.92 (0.82–1.03)	0.90 (0.80–1.01)
2–3 $\frac{1}{2}$	1.46 (1.10–1.94)	1.47 (1.10–1.95)	1.01 (0.87–1.16)	1.01 (0.87–1.17)
≥ 4	1.05 (0.54–2.04)	1.11 (0.57–2.17)	1.11 (0.83–1.47)	1.17 (0.88–1.55)
Late pregnancy				
Non-drinkers	1 (reference)	1 (reference)	1 (reference)	1 (reference)
$\frac{1}{2}$	0.96 (0.72–1.27)	0.91 (0.69–1.22)	1.09 (0.96–1.24)	1.04 (0.92–1.18)
1–1 $\frac{1}{2}$	1.31 (1.04–1.65)	1.26 (1.00–1.59)	1.18 (1.05–1.31)	1.13 (1.01–1.26)
2–3 $\frac{1}{2}$	1.38 (1.06–1.79)	1.33 (1.02–1.73)	1.06 (0.93–1.21)	1.02 (0.90–1.17)
≥ 4	1.54 (1.00–2.37)	1.59 (1.03–2.46)	1.01 (0.80–1.29)	1.05 (0.82–1.33)

*Unadjusted HR (95% confidence interval (CI)) obtained by Cox regression.

†HR (95% CI) obtained by Cox regression adjusted for sex, maternal age, occupational class of the mother, educational level of the mother, household income, breastfeeding, parental allergic disease, smoking during and after pregnancy, pets in the home, birth season, number of siblings, gestational age, birth weight, and head circumference.

AD, atopic dermatitis; HR, hazard ratio.

Stratification by parental allergic disease showed that the effect of alcohol consumption at 30 weeks of gestation on the risk of early-onset AD appeared to be dependent on the level

of parental allergic disease (Table 3 and Fig. 1). Similar results were seen for alcohol consumption at 12 weeks of gestation (data not shown). Thus, in high-risk children (two

Table 3. The relationship of alcohol consumption at 30 weeks of gestation to the incidence of AD during the first 60 days of life and during 2–18 months of life stratified by parental allergic disease

Alcohol consumption (drinks/week)	The effect of alcohol on AD at 0–2 months of life Adjusted HR*	The effect of alcohol on AD at 2–18 months of life Adjusted HR*
No parent with allergic disease (<i>n</i> = 11 357 infants)		
Non-drinkers	1 (reference)	1 (reference)
$\frac{1}{2}$	0.85 (0.52–1.39)	1.06 (0.84–1.32)
1–1 $\frac{1}{2}$	0.99 (0.65–1.50)	1.32 (1.09–1.59)
2–3 $\frac{1}{2}$	1.01 (0.63–1.62)	1.09 (0.87–1.37)
≥ 4	1.10 (0.51–2.39)	1.06 (0.72–1.57)
One parent with allergic disease (<i>n</i> = 10 218 infants)		
Non-drinkers	1 (reference)	1 (reference)
$\frac{1}{2}$	0.86 (0.56–1.31)	0.98 (0.82–1.17)
1–1 $\frac{1}{2}$	1.22 (0.88–1.70)	1.08 (0.92–1.26)
2–3 $\frac{1}{2}$	1.36 (0.93–1.98)	1.00 (0.82–1.21)
≥ 4	1.43 (0.74–2.75)	1.14 (0.82–1.58)
Two parents with allergic disease (<i>n</i> = 2616 infants)		
Non-drinkers	1 (reference)	1 (reference)
$\frac{1}{2}$	1.26 (0.64–2.47)	1.19 (0.89–1.60)
1–1 $\frac{1}{2}$	2.13 (1.24–3.64)	0.92 (0.68–1.24)
2–3 $\frac{1}{2}$	2.07 (1.13–3.77)	0.96 (0.69–1.34)
≥ 4	4.15 (1.71–10.07)	0.62 (0.25–1.52)

*HR (95% confidence interval) obtained by Cox regression adjusted for sex, maternal age, occupational class of the mother, educational level of the mother, household income, parental allergic disease, breastfeeding, smoking during and after pregnancy, pets in the home, birth season, number of siblings, gestational age, birth weight, and head circumference.
AD, atopic dermatitis; HR, hazard ratio.

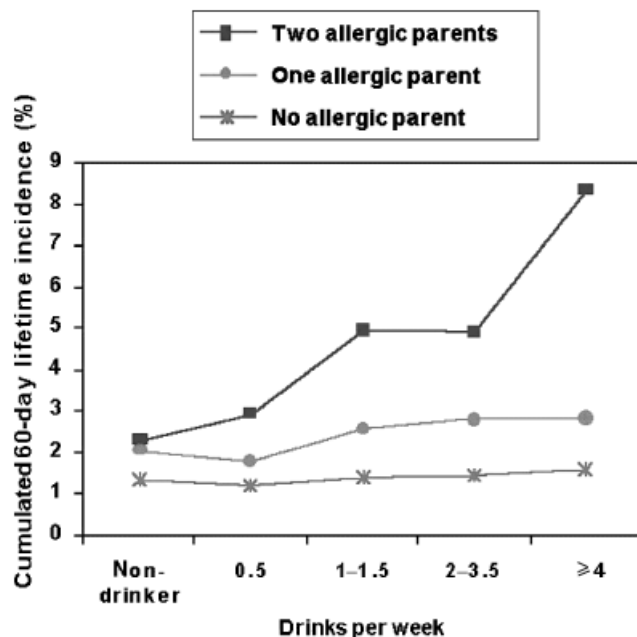


Fig. 1. The relationship of alcohol consumption at 30 weeks of gestation to the cumulated 60-day lifetime incidence (in percent) of atopic dermatitis stratified by level of parental allergic disease.

parents with allergic disease) alcohol during pregnancy conferred a dose-dependent significantly increased risk of AD in early infancy.

In further analyses, it was shown that consumption of wine and spirits appeared to account for the positive

association between alcohol consumption during pregnancy and development of AD in early infancy (data not shown).

Discussion

We found that alcohol consumption during pregnancy was associated with an increased risk of early onset AD. This was mainly seen in predisposed infants.

It should be considered whether the association between alcohol consumption during pregnancy and AD in early infancy could be due to confounding by other factors. However, adjustment for several potential confounders did not change the estimates for the effect of alcohol consumption substantially (Table 2). Residual or unmeasured confounding cannot be totally excluded. Of note is that alcohol consumption before pregnancy was not associated with the incidence of AD in early infancy, which might support that the observed effect of alcohol during pregnancy reflects a biological effect rather than being because of confounding.

Misclassification of AD is inevitable in interview-based studies. The diagnosis of AD was based on a set of diagnostic criteria, which we have found to be robust and reasonably specific [15]. It should be recognized that information on early-onset AD obtained when the child was 18 months of age may be subject to misclassification. However, we have no reason to believe that any misclassification of AD would be related to alcohol consumption during pregnancy. Assessment of alcohol intake by interview probably underestimates the true alcohol intake. At present, there is no generally accepted biomarker of alcohol consumption in population-based studies, and this remains a general limitation of studies of health effects of alcohol consumption. Since the data were collected prospectively and there was no prior knowledge of the hypothesis under study, differential misclassification seems unlikely. Thus, assuming that any misclassification of AD and alcohol consumption is non-differential, this would tend to underestimate an association, if present, between alcohol and AD.

Although antenatal factors have been implicated in the maturation of the innate immune response and the development of AD [9], little is known about the role of maternal lifestyle factors during pregnancy. Macaubas et al. [13] reported that detectable cord blood concentrations of IL-4 and INF- γ predicted the development of asthma and skin prick test reactivity against inhalant allergens at 6 years suggesting factors that influence cytokine production by the fetoplacental unit may be important determinants of atopic disease. Bjerke et al. [17] investigated the influence of environmental factors on levels of total IgE in cord blood of 2631 newborn infants. They found an independent positive dose-response relationship between maternal alcohol consumption during pregnancy and levels of cord blood IgE. Because of the apparent ability of alcohol to increase serum total IgE, it could be of interest to discriminate between IgE- and non-IgE-associated AD. In the present study, this was not possible. Ahluwalia et al. [18] found increased levels of cytokines, e.g. IL-1- β , IL-6 and TNF- α , in cord blood of the offspring of mothers with chronic (but not moderate) use of alcohol as compared with non-users.

Experimental studies in rats have shown that alcohol consumption during pregnancy increases levels of histamine, a key mediator in atopic disease, in the blood and the brain of both the fetus and the newborn rat [19]. Levels of histamine returned to control values after birth. In adults, alcoholic drinks are well-known potential triggers of allergic and asthmatic reactions, although the mechanisms are not fully understood [20, 21]. A histamine-releasing effect of acetaldehyde, a metabolite of ethanol, represents a conceivable mechanism for these reactions. This has primarily been shown in Oriental asthmatics [22], who have a high frequency of a genetic polymorphism of acetaldehyde dehydrogenase 2 (ALDH2), which is associated with low ALDH2 activity [23]. The role of this mechanism in Caucasians remains to be investigated. The frequency of the above polymorphism is very low in Caucasians, but polymorphisms of other genes encoding for enzymes in alcohol metabolism might modify the effects of alcohol on the immune system. In the present study, a genetic predisposition, in terms of parental history of allergic disease, modified the effect of alcohol exposure, a finding that is consistent with the concept that gene-environment interaction plays a role in the development of atopic disease. Therefore, these data suggest that the effect of alcohol may only be important in the presence of a substantial genetic predisposition.

Excessive and even moderate consumption of alcohol increases levels of serum total IgE, as reviewed by González-Quintela et al. [24]. Recently, population-based studies have confirmed this effect [25, 26]. Data from The Copenhagen Allergy Study, a population-based study in adults, have indicated a positive association of alcohol consumption with the prevalence [27] and incidence [25] of IgE sensitization against inhalant allergens. However, at present the epidemiological evidence is limited and the underlying mechanisms remain to be elucidated [28]. In animal studies, it has been shown that alcohol has an influence on immune responses and induces polarization of the immune response towards T-helper type 2 lymphocyte dominance [29, 30].

We found that the effect of alcohol during pregnancy on the incidence of AD was present in early infancy (first 60 days of life), but not beyond this period. This is consistent with the notion that the effect of alcohol on the fetal immune system is transient and attenuates after ceased exposure to alcohol at birth where the maternal and fetal circulations are separated. The alcohol-mediated increase in serum IgE in alcoholics also appears to be transient, since serum IgE decreases within weeks from the time of alcohol abstinence [24]. Accordingly, the increased levels of histamine in the blood of the newborn offspring of ethanol-fed rats returned to control values after birth [19]. Thus, a priori, we hypothesized that the effect of alcohol exposure during gestation on the risk of AD would possibly differ between early and late infancy. The cut-off of 2-months for early onset AD was arbitrarily chosen. However, the results were essentially similar, when a cut-off of 3 months was chosen (data not shown).

Restriction of alcohol consumption during pregnancy is recommended to reduce the risk of spontaneous abortion, stillbirth, low birth weight, malformations, and mental retardation. The present study suggests that this may also decrease the risk of early-onset AD in predisposed infants. More studies on the effects of alcohol during pregnancy

on early immune responses and risk of early-onset AD are warranted.

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