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Predicting skin barrier dysfunction and atopic dermatitis in early infancy

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Abstract:	Background Dry skin, associated with increased transepidermal water loss (TEWL), is found to precede atopic dermatitis (AD) in childhood. Objective We aimed to identify parental, prenatal and perinatal predictive factors of dry skin, high TEWL and AD at 3 months of age, and to determine if dry skin or high TEWL at 3 months can predict AD at 6 months.Methods From the Preventing Atopic Dermatitis and Allergies in children (PreventADALL)

	prospective birth cohort study, we included 1150 mother-child pairs. Dry skin, TEWL and eczema were assessed at 3- and 6 months investigations. Eczema, used as a proxy for AD, was defined as the presence of eczematous lesions, excluding differential diagnoses to AD. High TEWL was defined as TEWL > 90 th percentile, equalling 11.3 g/m 2 /h. Potential predictive factors were recorded from electronic questionnaires at 18- and 34-week pregnancy and obstetric charts. Results Significant predictive factors ($p<0.05$) for dry skin at 3 months were delivery > 38 gestational weeks and paternal age > 37 years, for high TEWL; male sex, birth during winter season and maternal allergic disease, and for eczema; elective caesarean section, multiparity, and maternal allergic diseases. Dry skin without eczema at 3 months was predictive for eczema at 6 months, (OR adjusted : 1.92, 95% CI: 1.21-3.05, $p=0.005$), while high TEWL at 3 months was not.Conclusion In early infancy, distinct parental and pregnancy-related factors were predictive for dry skin, high TEWL and AD. Dry skin at 3 months of age was predictive for AD three months later.

Predicting skin barrier dysfunction and atopic dermatitis in early infancy

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Abstract

Background

Dry skin, associated with increased transepidermal water loss (TEWL), is found to precede atopic dermatitis (AD) in childhood.

Objective

We aimed to identify parental, prenatal and perinatal predictive factors of dry skin, high TEWL and AD at 3 months of age, and to determine if dry skin or high TEWL at 3 months can predict AD at 6 months.

Methods

From the Preventing Atopic Dermatitis and Allergies in children (PreventADALL) prospective birth cohort study, we included 1150 mother-child pairs. Dry skin, TEWL and eczema were assessed at 3- and 6 months investigations. Eczema, used as a proxy for AD, was defined as the presence of eczematous lesions, excluding differential diagnoses to AD. High TEWL was defined as TEWL > 90th percentile, equalling 11.3 g/m^2/h. Potential predictive factors were recorded from electronic questionnaires at 18- and 34-week pregnancy and obstetric charts.

Results

Significant predictive factors ($p<0.05$) for dry skin at 3 months were delivery > 38 gestational weeks and paternal age > 37 years, for high TEWL; male sex, birth during winter season and maternal allergic disease, and for eczema; elective caesarean section, multiparity, and maternal allergic diseases. Dry skin without eczema at 3 months was predictive for eczema at 6 months, ($OR_{adjusted}$: 1.92, 95% CI: 1.21-3.05, p=0.005), while high TEWL at 3 months was not.

Conclusion

In early infancy, distinct parental and pregnancy-related factors were predictive for dry skin, high TEWL and AD. Dry skin at 3 months of age was predictive for AD three months later.

Short title: Prediction of skin barrier dysfunction and AD in infants

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Clinical implications: Recognizing dry skin in early infancy could be a way of selecting infants for primary prevention of atopic dermatitis.

Highlight box:

1. What is already known about this topic?

Skin barrier dysfunction, measured by increased transepidermal waterloss (TEWL) has been found to precede atopic dermatitis (AD). Dry skin, a cardinal sign of AD is associated with higher TEWL.

2. What does this article add to our knowledge?

The article reveals distinctive factors predictive for dry skin, high TEWL and AD at 3 months of age. Dry skin at 3 months was predictive for AD three months later.

3. How does this study impact current management guidelines?

Recognizing predictive factors for AD early in life, including the presence of dry skin, may help targeting infants for primary prevention of AD.

Key words: Dry skin, xerosis, skin barrier, atopic dermatitis, eczema, allergic diseases, atopy, TEWL

Abbreviations:
AD: atopic dermatitis

TEWL: transepidermal water loss

FLG: filaggrin

GA: gestational age

CS: Caesarean section

Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that most often present during early childhood (1). The lifetime prevalence in industrialized countries is high, ranging from 15-20% (2). Dry skin, erythema and pruritus are hallmarks of the disease (1). Diagnosis of AD is made clinically, sometimes using validated diagnostic criteria (3, 4).

The pathophysiological aspect of AD involves complex interactions between skin barrier function, immune dysregulation and dysbiosis of the skin microbiota (1, 5). A dysfunctional skin barrier appears to be a key player in development of the disease (1, 6). The clinical presence of dry skin, a cardinal feature of AD (1, 3, 4), is indicative of an impaired skin barrier and correlates with elevated measures of transepidermal water loss (TEWL) (7, 8). Recent studies suggest that increased TEWL in early infancy may precede and even predict the development of AD (9-11). Infants with AD are at increased risk of developing food allergy, allergic rhinitis and asthma in line with the proposed atopic march (12, 13). These findings provide a rationale for early life skin-directed treatment to enhance the barrier function and possibly prevent AD (14-16).

The most prominent risk factors for development of AD are parental allergic disease and the presence of mutations in the gene encoding filaggrin (*FLG*) (1, 6, 17). The most consistent environmental risk factors are low UV-light exposure, dry climate, urban living, small family size, high parental education level and repeated treatment with antibiotics in early childhood (17, 18). In addition, the association between caesarean section and offspring allergic disease has been extensively investigated, however with conflicting results (19-21). Increased knowledge of predictive factors of skin barrier dysfunction and AD in infancy is warranted to provide targeted prevention strategies. Studies aiming to identify predictors of dry skin and

reduced skin barrier function measured by TEWL in early infancy have largely been lacking. We are not aware of previous studies investigating the presence and distribution of dry skin and later debut of AD in early infancy.

We recently showed in the PreventADALL cohort that 59% of 3-month old infants had dry skin, while of the 145 infants with eczema 96% had dry skin. Dry skin without eczema on age specific predilection sites of AD, cheeks and extensor surfaces of extremities were significantly associated with increased TEWL (8).

In the present study we hypothesized that dry skin or increased TEWL could predict AD in infancy. We aimed to identify factors that can predict dry skin, high TEWL and AD at 3 months of age. Further, we aimed to determine if dry skin, in general or on age specific predilection sites of AD, or high TEWL at 3 months of age could predict AD at 6 months of age.

Subjects and Methods

Study design

The present study included 1150 infants, attending the 3 months investigation, randomized to the two groups that did not receive skin care intervention from the general population based Preventing Atopic Dermatitis and Allergies (PreventADALL) study (22). The PreventADALL multicentre, prospective, 2x2 factorial, interventional birth-cohort study investigates the effect of primary prevention of allergic diseases by early skin care and early complementary food introduction.

Women were recruited during the routine 18-week gestational age (GA) ultrasound examination at Oslo University Hospital, Østfold Hospital Trust (Norway) and Karolinska

University Hospital (Stockholm, Sweden) between December 2014 and October 2016. Their infants, born at a GA of at least 35 weeks and without serious illnesses, were enrolled during the 1-2 first days of life. Infants attended follow-up visits at 3 and 6 months of age, with skin assessments performed by trained study personnel who were blinded to the randomization groups. Study information included comprehensive electronic questionnaires, weekly diaries, biological samples from mother and child, and clinical investigations. Study design, recruitment and inclusion criteria, as well as characteristics of the 2696 women and 2396 mother-child pairs have been described in detail in a previous paper (22).

Informed consent forms were signed by the mother at enrollment, and by both parents (when relevant) upon inclusion of the infant. The PreventADALL study was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (2014/518) and in Sweden (2014/2242-31/4), as well as registered at clinicaltrials.gov (*NCT02449850).*

Subjects

The 1150 infants had a mean GA of 39.3 weeks at birth and 46.2% were girls (Table I).
For the secondary aim, we included all 930 of the 1070 infants who also attended the 6-month follow-up visit, excluding infants with eczema at the 3-month investigation, as shown in Figure 1. Detailed information on dry skin location at 3 months and eczema at 6 months was available in 913 infants.

Health personnel were trained to examine the skin by visual inspection and palpation. Observations of dry skin, presented as scaling and roughness, were recorded for 11 predefined anatomical skin areas (23) in terms of no, mild, moderate or severe dry skin. Severity of dry skin was recorded in line with the principles of the Dry skin/Ichtyosis and Severity Index (DASI), but without their score of erythema (24). *Mild dryness* was categorized as barely

visible scaling and slight roughness when stroking the skin. *Moderate dryness* was categorized as clearly visible scaling with or without fissures, and roughness when stroking the skin. *Severe dryness* was categorized as abundant scaling and present fissures, as well as very rough skin when stroking the skin.

Eczema, used as a proxy for AD, was defined as the presence of eczematous lesions, verified by a medical doctor with the exclusion of differential diagnoses to AD.

TEWL measurements ($g/m^2/h$) were available in 1033 (89%) of the 3 months old infants, using an open chamber DermaLab USB (Cortex, Hadslund, Denmark). We included measurements performed in room temperature between 20 and 25°C only, in line with international recommendations (25), while accepting humidity within the whole range 6% - 73%, mean 29%, standard deviation (SD) 12.7. Parents were instructed not to bathe the infants or use any emollients within 24 hours prior to the examination. Three successive measurements were performed on the left upper lateral arm after 15 minutes of acclimatization where the child was only wearing diaper, keeping the room temperature as close to 22°C as possible, noting ambient temperature and humidity. Measurements were only performed on calm children and windows and doors were kept shut.

Potential predictive factors were chosen on the basis of previously described risk factors for allergic diseases, potential relevant pregnancy-related factors as well as baseline characteristics as outlined in Table 1.

Definitions and outcome

Unaffected skin was defined as no eczema and no dry skin. *Dry skin* included all infants with presence of dry skin on at least one location, regardless of eczema. *Dry skin only* was defined

as dry skin with no eczema and was further sub-categorized into dry skin on *Cheeks*, *Extensors* or *Both cheeks and extensors.*

The outcomes in the present study were *Dry skin* (any location of dry skin), *Eczema* and *High TEWL* (mean TEWL above 90th percentile) at 3 months of age and *Eczema* at 6 months of age.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as means, SD and minimum (min) –maximum (max).

While the TEWL results did not display a perfect normal distribution, the deviation from normality was moderate, and we could therefore use parametric statistical methods for all our analyses. Independent sample t-test was used when comparing continuous variables, and chi-square test was used when comparing categorical variables.

Logistic regression analysis was used to investigate the associations between parental and pregnancy- related variables (Table I) and the outcome variables *Dry skin*, *Eczema* or *High TEWL*. We used univariate logistic regression analysis with a cut-off p-value of 0.2, followed by complete-case multivariate regression analysis. The continuous variables that were found to be significant in the univariate regression analysis were analysed as quartiles, with the lowest quartile as the reference value. If the strength of the association was higher in any quartile, we used the quartiles in the multivariate regression model. In each regression model the assumption underlying multivariate logistic regression analysis were checked and found to be adequately met.

In order to investigate the impact of dry skin and high TEWL at 3 months of age on eczema at 6 months of age, the following three regression models were performed: Model 1: Unadjusted. Model 2: The predictors from the multivariate logistic regression analyses at 3 months of age were used here. For dry skin we adjusted for the predictors found for dry skin and eczema, and for high TEWL we adjusted for the predictors found for high TEWL and eczema. Model 3: Variables from model 2 together with variables significantly associated with *Eczema* at 6 months from univariate logistic regression analysis (doctor diagnosed AD in father, alcohol consumption and domestic cat during pregnancy). Statistical significance level was set to 5%. All analyses were performed using IBM© SPSS© statistics version 25 (Chicago, IL, U.S.A.).

Results

Baseline characteristics

At 3 months of age 544 out of the 1150 infants investigated, had dry skin without eczema (dry skin only) and 145 had eczema. At 6 months of age 163 of the 930 infants that attended the follow-up had eczema, excluding the infants with eczema at 3 months. Out of 832 with valid TEWL measurements, 82 had high TEWL at 3 months. The clinical, socioeconomic, and demographic details of the study population are presented in Table I for the infants at 3 months of age and for the infants at 6 months are presented in Table EI in the online repository.

Predictive factors at 3 months of age

For *Dry skin*, GA and paternal age were statistical significant predictors in the multivariate analysis after including the 10 variables with a p-value <0.2 in the univariate logistic regression analysis (Figure 2a, Table E2a and E3a in the online repository). When analysed as continuous variables in univariate analyses, dry skin was significantly and positively associated with GA (OR: 1.16, CI 95%: 1.08-1.25; p<0.0001) and paternal age (OR: 1.05, CI 95%: 1.02-1.07; p=0.001). We analysed the predictive impact by categorising them into quartiles.

In multivariate analyses, compared to the lower quartile of GA (35.0-38.2), the highest OR (OR: 2.46, CI 95%: 1.60-3.79; p<0.0001) was found in the third quartile (GA 39.51 – 40.50), as shown in Figure 2a, Table E3a.

Similarly, for paternal age, the highest OR in multivariate analyses was found for the oldest age, with an OR: 1.96, CI 95%: 1.16-3.30; p=0.012 in the fourth compared to reference (lowest) quartile. Domestic cat exposure during pregnancy was a significant protective factor for dry skin in the multivariate analysis (OR: 0.55, CI 95%: 0.33-0.92; p=0.023).

For *High TEWL,* three variables were statistically significant in the multivariate analysis, namely female sex (OR: 0.61, CI 95%: 0.40-0.93; p=0.022), maternal allergic disease (OR: 1.80, CI 95%: 1.08-3.01; p=0.025) and birth during winter season (OR: 2.02, CI 95%: 1.31-3.14; p=0.002) (Figure 2b, Table E2b and E3b in the online repository), after including the six variables with a p-value < 0.2 in the univariate logistic regression analysis.

For *Eczema,* three variables were statistically significant in the multivariate analysis, namely elective caesarean section (OR: 2.50, CI 95%: 1.19-5.25; p=0.016), multiparity (one or more previous deliveries) (OR: 1.63, CI 95%: 1.03-2.57; p=0.037) and maternal allergic disease (OR: 1.61, CI 95%: 1.02-2.55; p=0.041) (Figure 2c, Table E2c and E3c in the online repository), after including 10 variables with a p-value <0.2 in the univariate logistic regression analysis. Paternal allergic disease was statistically significant in the univariate analysis (OR: 1.46, CI 95%: 1.01-2.13; p=0.046), as well as birthweight in the fourth quartile > 3.9 kg (OR: 1.89, CI 95%: 1.14-3.13; p=0.014) compared to reference (lowest quartile).

Dry skin or _High TEWL_ and _Eczema_ at 6 months of age

Infants who at 3 months of age had *Dry skin only,* regardless of location were significantly more often diagnosed with *Eczema* at 6 months of age (21.7%) compared to the infants with *Unaffected skin* (12.4%) (Figure 3), giving an unadjusted OR (95% CI) of 1.96 (1.37-2.80)

(p<0.0001). *Dry skin* at 3 months increased the risk of *Eczema* at 6 months by an OR (CI 95%) of 1.92 (1.21-3.05) (p=0.005) in the multivariate analysis adjusting for elective caesarean section, GA at birth, multiparity, paternal age, maternal allergic disease, paternal allergic disease, paternal atopic dermatitis, alcohol consumption during pregnancy and domestic cat during pregnancy. Similar risk was observed using dry skin in the cheeks and/or the extensors, OR (CI 95%) of 1.94 (1.20-3.15; p=0.007), adjusted for the same nine variables. The prediction of *Eczema* 6 months of age with *Dry skin* at 3 months of age had a sensitivity of 68% and a specificity of 48%.

Mean TEWL ($g/m^2/h$) in 3 month-old infants was not significantly associated with *Eczema* at 6 months as a continuous variable or by quartiles in univariate or multivariate analysis. *High TEWL* was significantly associated with *Eczema* at 6 months of age compared to mean TEWL <90^{th} percentile (N=750) (OR: 1.80, CI 95 %: 1.07-3.04; p=0.028) in univariate analysis, but did not remain statistically significant after adjustment for relevant factors outlined in Table E3 in the online repository.

Discussion

In the present population-based prospective mother-child cohort we found increased paternal age and GA at birth to be predictive of dry skin at 3 months of age, and maternal allergic disease, male sex and birth season were predictive for high TEWL (> 90^{th} percentile). For eczema at 3 months the predictors were elective caesarean section, at least one previous delivery, and maternal allergic disease. Dry skin at 3 months of age predicted AD at 6 months of age.

Our finding of increased GA as well as paternal age as predictors for dry skin has to our knowledge not previously been assessed. As dry skin is a main feature of AD, our findings are

supported by reports of increasing GA being associated with AD (26-28). The highest risk for dry skin was found among our children with the highest GA at birth, in line with reports of inverse associations between prematurity (GA<29 weeks) and AD (29, 30). These findings may be explained by shorter exposure time to the maternal immune system and Th2 cytokines, lower levels of IgE and a different composition of early gut and skin microbiome (26, 28, 29). Post-term neonatal skin having less vernix may experience longer direct exposure to amniotic fluid, which can disrupt the stratum corneum lipid bilayer (31, 32), and promote post-term skin dryness and higher TEWL values. Pregnancy length may thus be implicated in the skin integrity (28, 29). Our finding of advanced paternal age, especially above 37 years, being a predictor for dry skin, is to our knowledge novel, and could reflect a possible age related increase in mutations (33).

The protective effect of female sex on high TEWL is supported by previous findings that males have an earlier onset of AD compared to females (28, 34). Similarly to our study, a recent Japanese study found significantly higher TEWL in male infants (35). In contrast, TEWL in neonates was indistinguishable between males and females in an Indian study (36). Our findings that infants born during fall and winter season had higher TEWL at 3 months of age than those born during spring or summer is supported by reports that birth during fall and winter has been associated with increased risk of AD (30, 37, 38). These findings may be explained by cold climate and low environmental humidity that have been associated with impaired skin barrier function (18, 37, 39-41). Exposure to a dry and cold winter climate may lead to depletion of filaggrin and other skin barrier proteins as well as lipids (18, 42) and by lower cumulative UV irradiation before and after birth (37).

Our finding that multiparity was a predictor of AD at 3 months is in contrast to one of the key arguments for the hygiene hypothesis where having older siblings reduces the risk of AD (43),

but more in agreement with a study showing that the risk of AD was not reduced by having older siblings (44). In that study a higher prevalence of eczema in children carrying *FLG* mutations was found if they had older siblings (44), supported by larger sibships increasing the risk of severe AD (43). Parental allergic disease, a well-known risk factor for offspring AD (1, 17), was also a predictor of AD in our population. In our cohort, elective caesarean section was predictive of eczema at 3 months, while acute caesarean section was not. To our knowledge, this is the first study reporting on elective caesarean section being a predictor of AD in early infancy. The vast majority of the elective caesarean sections were prior to rupture of amniotic membranes and we hypothesize that a lacking exposure to the vaginal flora in elective caesarean sections (without rupture of amniotic membranes) (45) may contribute to an offspring gut and skin microbiome dysbiosis associated with AD (5). Our results may imply that onset of AD by 3 months of age, may be dominated by a genetic predisposition to allergic disease, but may be modified by mode of delivery and exposure to maternal vaginal flora.

Dry skin, but not TEWL at 3 months being a predictor of AD at 6 months, has to our knowledge not previously been reported. There are no direct comparable studies, nonetheless dry skin is a cardinal sign of AD (1, 8, 42, 46), and we (8) and others (47) have demonstrated that infants with dry skin have increased TEWL. In the present study the risk of AD at 6 months was particularly noticeable with dry skin on the cheeks and/or on the extensor surfaces of extremities at 3 months of age. Eczema of the cheeks is often the first manifestation of AD, and a recent Irish study by McAleer et al. (48) demonstrated that in 188 infants the skin of the cheeks were slower to mature than the skin of the nasal tip and elbow creases, and had lower levels of natural moisturizing factor. This indicates that early-onset AD may be due to a physiological skin barrier dysfunction restricted to a specific body location, possibly enhanced by factors such as male sex, birth season, and various environmental factors.

Although high TEWL at 3 months did not predict eczema at 6 months after adjusting for potential confounders, it remains to be investigated whether TEWL can predict AD at later time-points (9-11) in our cohort. The presence of clinically dry skin could precede AD without increased TEWL. Although our findings support the outside-inside hypothesis of AD (42), dry skin at 3 months as a predictor of AD at 6 months has low sensitivity and specificity and cannot be used as a single predictive tool for such a heterogeneous disease as AD (49, 50). In line with the concept of the atopic march (12, 13), or the association between dry skin and asthma in adults (51) early identification of dry skin may be useful as screening for targeted primary prevention provided that skin barrier enhancement is effective in reducing AD.

The strengths of our study include a large prospective cohort study from a general population, with high follow-up rate and stringent skin assessment by trained personnel as well as TEWL measurements, and parental risk factors prospectively recorded during pregnancy. The majority of the study participants originate from Nordic countries, which may to some extent limit the generalizability (52). Our study had several limitations including, infants only born from 35 week of GA, genetic analysis including *FLG* mutations were not available, and we could not use the UK Working Party criteria for AD (4) at this age, mainly due to difficulties in evaluating the infants sensation of itch. The relatively high number of possible predictors for the 3-month outcomes included in the analysis together with possible bias of missing data introduces a risk of false positive results. This must be taken into account when interpreting the results.

In conclusion, at 3 months of age, increasing paternal age and gestational age at birth were predictive for dry skin. Maternal allergic disease, male sex and winter birth season were predictive for high TEWL, while for eczema the predictors were elective caesarean section, at least one previous delivery, and maternal allergic disease. Dry skin at 3 months of age,

predicting AD at 6 months of age, may represent a factor in targeting infants for primary prevention of AD and possibly also food allergy and asthma.

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Table 1. Baseline characteristics for pregnancy variables in 1150 infants attending the 3-month investigation, where 'Unaffected skin' are infants without dry skin and eczema is defined as the presence of eczematous lesions, excluding differential diagnosis to atopic dermatitis (AD). Table 1a display parental variables, while Table 1b display prenatal and perinatal variables as well as variables related to the 3-month investigation.

Table 1a

Characteristics	Unaffected skin (N=461)	Dry skin (N=683) (139 with eczema)	Dry skin only (N=544)	Eczema (N=145)	Total (N=1150)
Age mother (years), mean, (SD, min-max)(N=1150)	32.1 (4.1, 21.0-48.0)	32.9 (4.1, 21.0-47.0)	32.8 (4.1, 21.0-47.0)	33.2 (4.2, 22.0-43.0)	32.6 (4.1, 21.0-48.0)
Age father (years), mean, (SD, min-max)(N=983)	34.0 (5.0, 21.0-53.0)	35.3 (5.4, 21.0-72.0)	35.2 (5.4, 21.0-72.0)	35.3 (5.5, 23.0-55.0)	34.8 (5.3, 21.0-72.0)
Mother Nordic origin N (%)(N=1046)	405 (93.8)	545 (89.5)	433 (89.3)	117 (90.7)	955 (91.3)
Father Nordic origin N (%)(N=1026)	386 (90.8)	525 (88.1)	419 (88.6)	111 (86.7)	916 (89.3)
Education mother, > 4 years of University, N (%)(N=1040)	239 (55.5)	371 (61.4)	299 (62.2)	73 (57.0)	611 (58.8)
Education co-parent, > 4 years of University, N (%)(N=1001)	201 (48.8)	294 (50.3)	237 (51.0)	59 (47.6)	497 (49.7)
Family income N (%)(N=1032)*					
Low	69 (16.2)	82 (13.6)	67 (14.0)	17 (13.4)	153 (14.8)
Middle	318 (74.6)	431 (71.7)	345 (72.0)	88 (69.3)	751 (72.8)
High	39 (9.2)	88 (14.6	67 (14.0)	22 (17.3)	128 (12.4)
Single mother N (%)(N= 1038)	6 (1.4)	11 (1.8)	8 (1.6)	3 (2.4)	17 (1.6)
BMI, mother at 18 weeks of pregnancy, mean, (SD, min-max)(N=1132)	24.7 (3.7, 17.2-39.7)	24.8 (3.7, 18.4-41.4)	24.8 (3.6, 18.4-39.5)	25.2 (4.0, 19.4-41.4)	24.8 (3.7, 17.2-41.4)
≥ 1 previous parity N (%)(N=1046)	161 (37.3)	264 (43.3)	199 (41.0)	70 (54.3)	430 (41.1)
Allergic disease mother, N (%) (N=1046)	261 (60.4)	408 (67.0)	318 (65.6)	94 (72.9)	673 (64.3)
Allergic disease father, N (%) (N=1048)	217 (51.1)	304 (49.1)	228 (46.4)	77 (58.3)	522 (49.8)
Atopic dermatitis mother, doctor diagnosed N (%)(N=1046)	83 (19.2)	132 (21.7)	101 (20.8)	32 (24.8)	216 (20.7)
Atopic dermatitis father, doctor diagnosed N (%)(N=1048)	48 (11.3)	67 (10.8)	46 (9.4)	22 (16.7)	116 (11.1)
Asthma mother, doctor diagnosed N (%)(N=1046)	79 (18.3)	106 (17.4)	84 (17.3)	24 (18.6)	187 (17.9)
Asthma father, doctor diagnosed N (%)(N=1048)	64 (15.1)	79 (12.8)	61 (12.4)	19 (14.4)	144 (13.7)
Allergic rhinitis mother, doctor diagnosed N (%)(N=1046)	77 (17.8)	142 (23.3)	115 (23.7)	29 (22.5)	221 (21.1)
Allergic rhinitis father, doctor diagnosed N (%)(N=1048)	93 (21.9)	149 (24.1)	114 (23.2)	36 (27.3)	243 (23.2)
Food allergy mother, doctor diagnosed N (%)(N=1046)	56 (13.0)	81 (13.3)	67 (13.8)	14 (10.9)	137 (13.1)
Food allergy father, doctor diagnosed N (%)(N=1048)	34 (8.0)	59 (9.5)	48 (9.8)	12 (9.1)	94 (9.0)

Table 1b

Characteristics	Unaffected skin (N=461)	Dry skin (N=683) (139 with eczema)	Dry skin only (N=544)	Eczema (N=145)	Total (N=1150)
Lifestyle during pregnancy					
Alcohol intake N (%)(N=914)	22 (5.1)	42 (7.7)	29 (6.0)	13 (10.1)	64 (7.0)
Tobacco use in general N (%)(N=1128)	54 (11.8)	66 (9.9)	54 (10.2)	13 (9.2)	121 (10.7)
Smoking N (%)(N=1128)	24 (5.3)	26 (3.9)	19 (3.6)	8 (5.7)	51 (4.5)
Snus use N (%)(N=1128)	34 (7.5)	42 (6.3)	37 (7.0)	5 (3.5)	76 (6.7)
Live rural N (%)(N=1046)	40 (9.3)	50 (8.2)	43 (8.9)	7 (5.4)	90 (8.6)
Exposure to humidity/mould N (%)(N=984)	51 (12.5)	83 (14.6)	69 (15.3)	16 (13.0)	136 (13.8)
Pets in general N (%)(N=1046)	116 (26.9)	133 (21.8)	105 (21.6)	29 (22.5)	250 (23.9)
Cat, no dog N (%)(N=1046)	48 (11.1)	41 (6.7)	30 (6.2)	12 (9.3)	90 (8.6)
Dog, no cat N (%)(N=1046)	53 (14.0)	70 (11.5)	59 (12.2)	11 (8.5)	123 (11.8)
Cat and dog N (%)(N=1046)	6 (1.4)	10 (2.0)	8 (1.6)	2 (1.6)	15 (1.4)
Pets except cat and dog N %)(N=1046)	9 (2.1)	12 (2.0)	8 (1.6)	4 (3.1)	22 (2.1)
Caesarean section, N (%)(N=1137)	69 (15.2)	106 (15.6)	80 (14.8)	27 (18.8)	176 (15.5)
Elective N (%)(N=1137)	22 (4.9)	42 (6.2)	30 (5.6)	12 (8.3)	64 (5.6)
Acute N (%)(N=1137)	47 (10.4)	64 (9.4)	50 (9.3)	15 (10.4)	112 (9.9)
Gestational age at birth (weeks), mean (SD, min-max) (N=1128)	39.1 (1.8, 35.0-42.9)	39.5 (1.6, 35.1-42.9)	39.6 (1.6, 35.1-42.9)	39.5 (1.6, 35.2-42.2)	39.3 (1.7, 35.0-42.9)
Female sex N (%) (N=1146)	221 (48.1)	307 (45.1)	251 (46.3)	58 (40.0)	530 (46.2)
Birth weight (kg), mean, (SD, min-max) (N=1114)	3.5 (0.5, 1.9-5.1)	3.6 (0.5, 2.1-5.0)	3.6 (0.5, 2.1-4.9)	3.7 (0.5, 2.6-5.0)	3.6 (0.5, 1.9-5.1)
Born during winter season (October – March) N (%)(N=1146)	238 (51.9)	392 (57.6)	306 (56.5)	87 (60.0)	631 (55.1)
3-month investigation					
Age (days), mean (SD, min-max) (N=1145)	94 (9.4, 55-150)	93 (7.6, 69-134)	93 (7.9, 69-134)	94 (6.4, 83-112)	93 (8.4, 55-150)
Weight (kg), mean, (SD, min-max) (N=1118)	6.2 (0.8, 4.4-9.3)	6.3 (0.8, 4.2-8.9)	6.3 (0.8, 4.2-8.7)	6.3 (0.7, 4.4-8.9)	6.3 (0.8, 4.2-9.3)
Length (cm), mean, (SD, min-max) (N=1125)	61.7 (2.4, 54.0-70.9)	62.0 (2.3, 51.0-69.5)	62.0 (2.3, 51.0-69.5)	62.1 (2.2, 56.8-68.5)	61.9 (2.3, 51.0-70.9)
TEWL ($g/m^2/h$) mean, (SD, min-max) (N=1026)	6.7 (3.5, 1.3-32.6)	8.5 (6.3 (1.6-46.2)	7.6 (5.3, 1.6-46.2)	12.4 (8.9, 3.3-45.2)	7.8 (5.5, 1.3-46.2)

Figure legend

Figure 1. Outline of children in the present study are based upon the source population of the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) with 2701 pregnancies included, resulting in a birth-cohort of 2396 mother-child pairs.

Figure 2. Significant predictors ($p < 0.05$) for dry skin (2a), TEWL > 90th percentile (11.3 $g/m^2/h$) (2b) and eczema (2c) at 3 months of age in 1150 infants, when using multivariate regression analysis shown as odds ratio and confidence intervals.

2a Pregnancy variables with cut-off p-value of < 0.2 for predicting dry skin used in the multivariate analysis were: GA at birth, birth weight, multiparity, domestic cat exposure, maternal age, paternal age, maternal allergic disease, maternal education, family income and birth season.

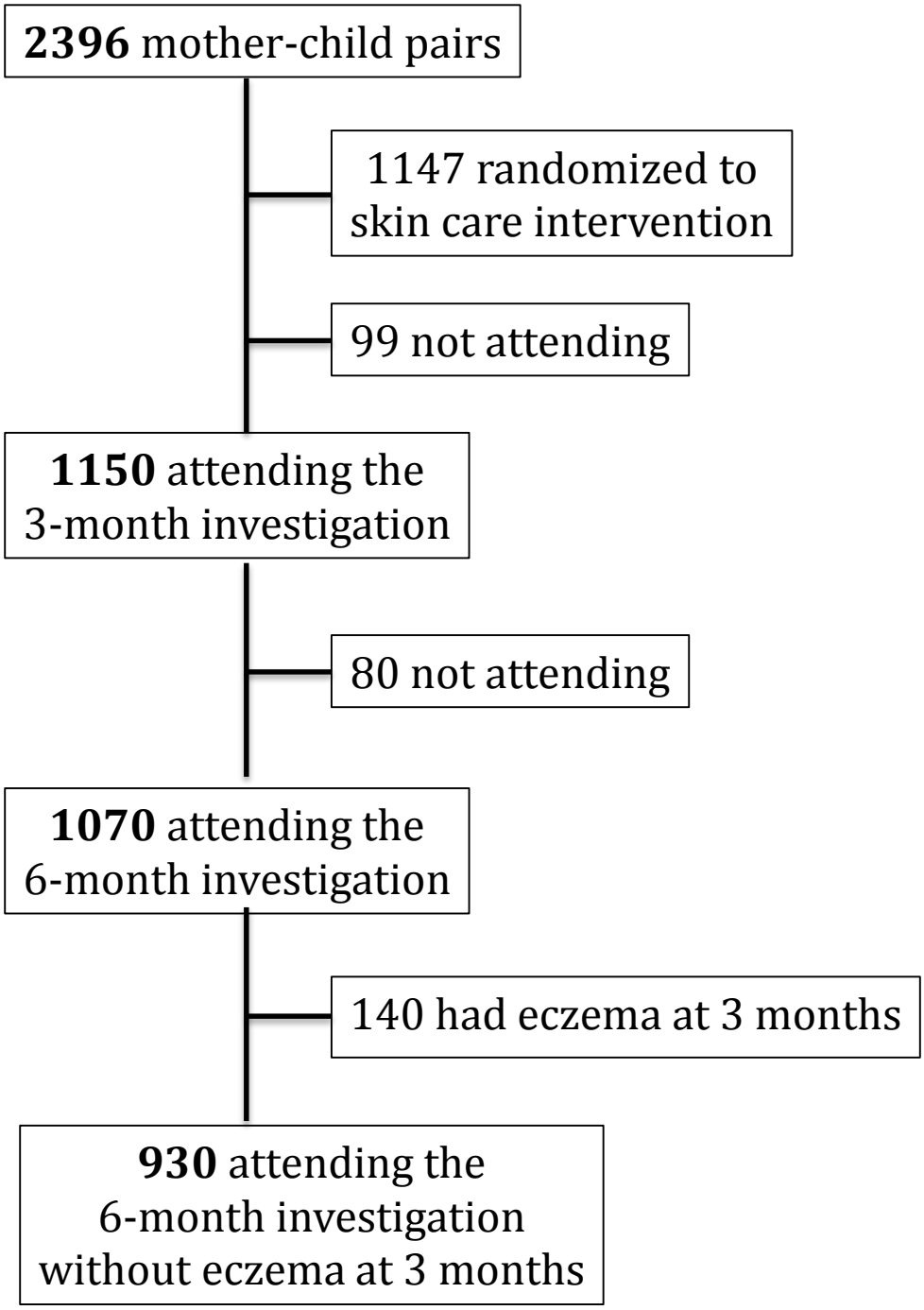
2b Pregnancy variables with cut-off p-value of < 0.2 for predicting TEWL > 90th percentile (11.3 $g/m^2/h$) used in the multivariate analysis were: female sex, birth weight, maternal allergic disease, maternal atopic dermatitis, and birth season.

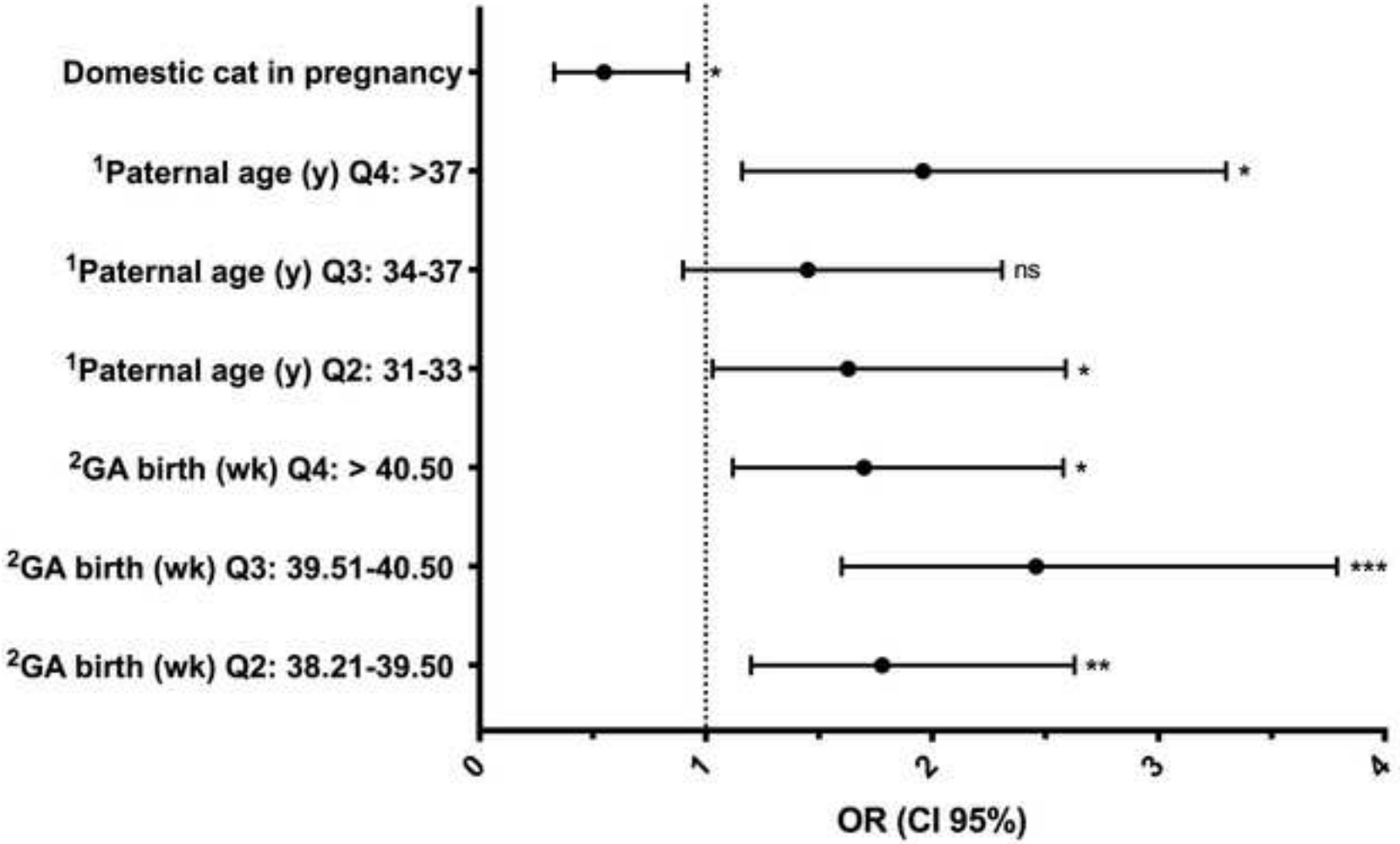
2c Pregnancy variables with cut-off p-value of < 0.2 for predicting eczema, defined as the presence of eczematous lesions, excluding differential diagnosis to atopic dermatitis, used in the multivariate analysis were: female sex, birth weight, multiparity, elective caesarean section (CS), maternal age, maternal allergic disease, paternal allergic disease, snus during pregnancy, rural living and family income.

Figure 3. The Euler diagram depicts the distribution of dry skin at 3 months in 159 infants who at 6 months presented with eczema, used as a proxy for atopic dermatitis. Dry skin at 3 months, regardless of location was a significant predictor for atopic dermatitis at 6 months of age with an OR (CI 95%) of 1.92 (1.21-3.05) (p=0.005), and OR (CI 95%) of 1.94 (1.20-3.15; p=0.007) for dry skin in the cheeks and/or the extensors specifically at 3 months.

Footnote for Figure 3:
Produced with courtesy of: Luana Micallef and Peter Rodgers (2014). eulerAPE: Drawing Area-proportional 3-Venn Diagrams Using Ellipses. PLoS ONE 9(7): e101717. doi:10.1371/journal.pone.0101717. http://www.eulerdiagrams.org/eulerAPE

Figure No. 1 - Unmarked

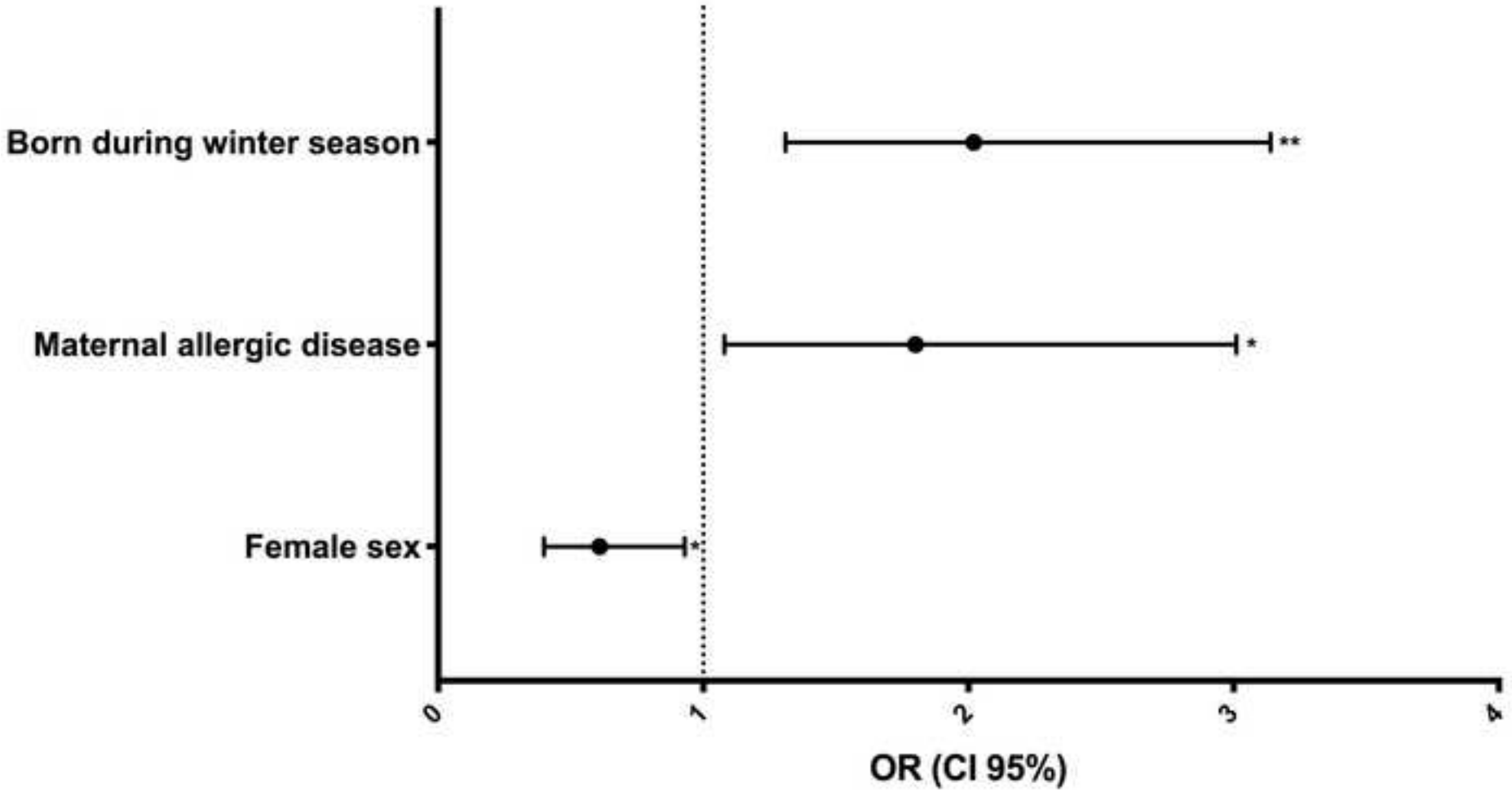




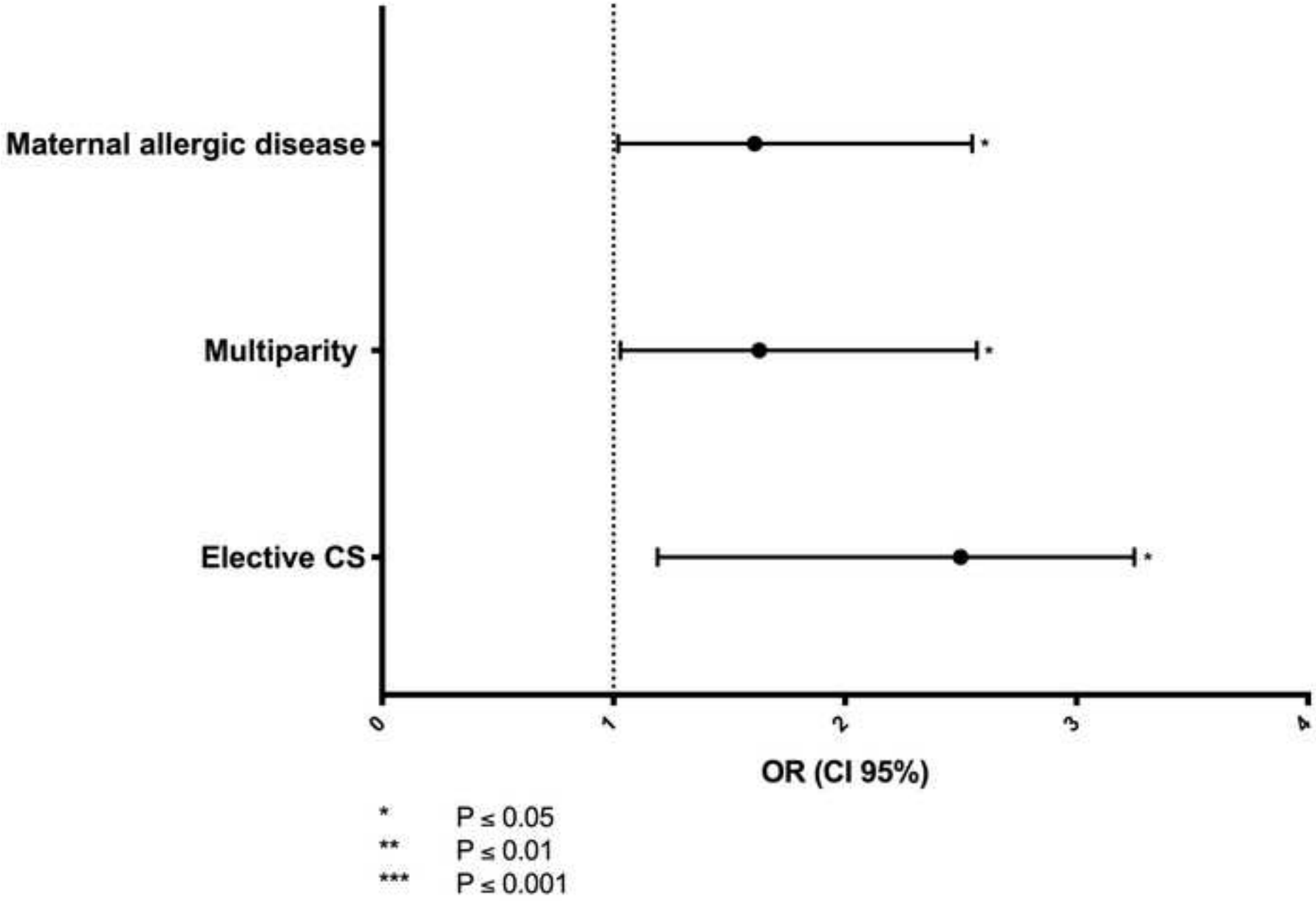
ns	not significant
*	P ≤ 0.05
**	P ≤ 0.01
***	P ≤ 0.001

[1]Paternal age in years divided in quartiles (Q), where the first quartile of 21-30 years is used as reference value.

[2]Gestational age (GA) at birth in weeks divided in quartiles (Q) where first quartile is 35.00-38.20 weeks and used as reference value.



* P ≤ 0.05
** P ≤ 0.01
*** P ≤ 0.001



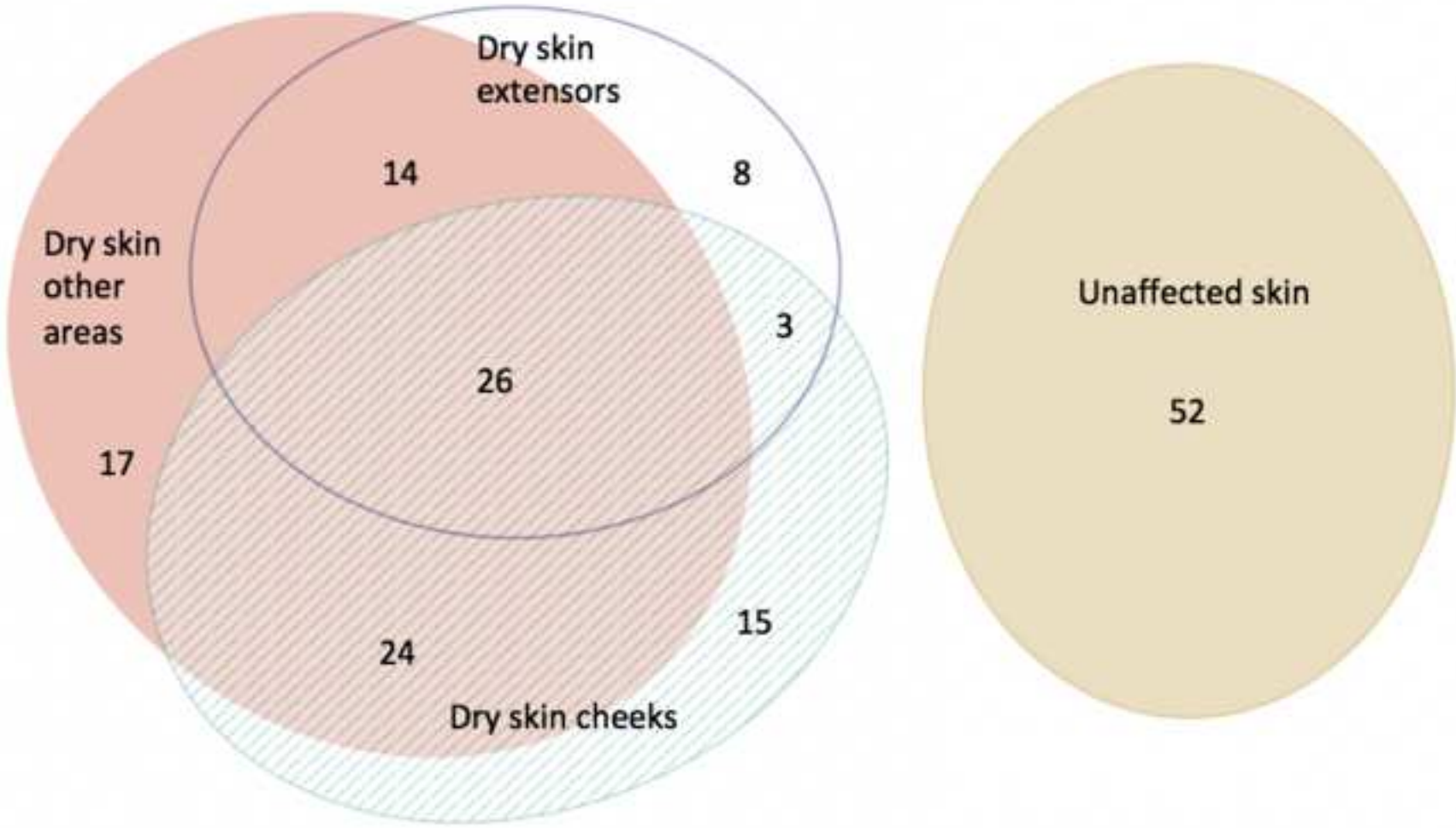


Table E1. Baseline characteristics in 930 infants attending 6-month investigation, grouped in to No eczema and Eczema, defined as the presences of eczematous lesions, excluding differential diagnosis to AD. Those with eczema at the 3-month investigation have been excluded.

Characteristics	No eczema 6 months (N=767)	Eczema 6 months (N=163)	Total (N=930)
Age mother (years), mean, (SD, min-max)(N=927)	32.6 (4.1, 21.0-47.0)	32.3 (3.7, 25.0-42.0)	32.5 (4.1, 21.0-47.0)
Age father (years), mean, (SD, min-max)(N=804)	34.8 (5.3, 21.0-72.0)	34.7 (5.1, 25.0-51.0)	34.8 (5.3, 21.0-72.0)
Mother Nordic origin N (%)(N=854)	648 (91.8)	135 (91.2)	783 (91.7)
Father Nordic origin N (%)(N=837)	621 (89.6)	128 (88.9)	749 (89.5)
Education mother, > 4 years of University, N (%)(N=849)	409 (58.3)	97 (65,5)	506 (59.6)
Education co-parent, > 4 years of University, N (%)(N=817)	344 (50.7)	68 (49.3)	412 (50.4)
Family income N (%)(N=842)			
Low	105 (15.1)	18 (12.2)	123 (14.6)
Middle	510 (73.4)	110 (74.8)	620 (73.6)
High	80 (11.5)	19 (12.9)	99 (11.8)
BMI, mother at 18 weeks of pregnancy, mean, (SD, min-max)(N=918)	24.8 (3.7, 18.3-39.5)	24.5 (3.2, 17.2-36.1)	24.8 (3.6, 17.2-39.5)
≥ 1 previous parity N (%)(N=854)	286 (40.5)	49 (33.1)	335 (39.2)
Allergic disease mother, N (%) (N=854)	449 (63.6)	94 (63.5)	543 (63.6)
Allergic disease father, N (%) (N=853)	334 (47.6)	82 (54.3)	416 (48.8)
Atopic dermatitis mother, doctor diagnosed N (%)(N=854)	141 (20.0)	28 (18.9)	169 (19.8)
Atopic dermatitis father, doctor diagnosed N (%)(N=774)	65 (10.1)	22 (16.5)	87 (11.2)
Asthma mother, doctor diagnosed N (%)(N=854)	123 (17.4)	28 (18.9)	151 (17.7)
Asthma father, doctor diagnosed N (%)(N=826)	96 (14.2)	22 (14.9)	118 (14.3)
Allergic rhinitis mother, doctor diagnosed N (%)(N=778)	150 (23.3)	26 (19.5)	176 (22.6)
Allergic rhinitis father, doctor diagnosed N (%)(N=781)	157 (24.3)	41 (30.6)	198 (25.4)
Food allergy mother, doctor diagnosed N (%)(N=808)	99 (14.8)	17 (12.2)	116 (14.4)
Food allergy father, doctor diagnosed N (%)(N=812)	60 (8.9)	15 (10.6)	75 (9.2)
Lifestyle during pregnancy			
Alcohol intake N (%)(N=774)	33 (5.4)	15 (11.3)	48 (6.5)
Tobacco use in general N (%)(N=915)	78 (10.4)	15 (9.3)	93 (10.2)
Smoking N (%)(N=915)	33 (4.4)	3 (1.9)	36 (3.9)
Snus use N (%)(N=915)	51 (6.8)	12 (7.4)	63 (6.9)
Live rural N (%)(N=854)	67 (9.5)	13 (8.8)	80 (9.4)
Exposure to humidity/mould N (%)(N=806)	87 (13.1)	27 (19.0)	114 (14.1)
Pets in general N (%)(N=854)	180 (25.5)	27 (18.2)	207 (24.2)
Cat, no dog N (%)(N=854)	69 (9.8)	5 (3.4)	74 (8.7)
Dog, no cat N (%)(N=854)	86 (12.2)	17 (11.5)	103 (12.1)
Cat and dog N (%)(N=854)	12 (1.7)	2 (1.4)	14 (1.6)
Pets except cat and dog N %)(N=854)	13 (1.8)	3 (2.0)	16 (1.9)
Caesarean section, N (%)(N=918)	104 (13.7)	27 (18.0)	133 (14.4)
Elective N (%)(N=918)	33 (4.4)	12 (7.5)	45 (4.9)
Acute N (%)(N=918)	71 (9.4)	17 (10.6)	88 (9.6)
Gestational age at birth (weeks), mean (SD, min-max) (N=913)	39.3 (1.7, 35.0-42.9)	39.4 (1.6, 35.2-42.9)	39.3 (1.7, 35.0-42.9)
Female sex N (%) (N=927)	370 (48.2)	70 (43.2)	440 (47.5)
Birth weight (kg), mean, (SD, min-max) (N=897)	3.6 (0.5, 1.9-4.9)	3.6 (0.5, 2.2-5.1)	3.5 (0.5, 1.9-5.1)
Born during winter season (October – March) N (%)(N=927)	429 (56.1)	84 (51.9)	513 (55.3)
6-month investigation			
Age (days), mean (SD, min-max) (N=927)	190 (13.5, 146-248)	189 (11.7, 155-224)	190 (13.2, 146-248)
Weight (kg), mean, (SD, min-max) (N=907)	8.1 (1.0, 5,3-11,9)	8.1 (1.0, 5.2-12.3)	8.1 (1.0, 5.2-12.3)
Length (cm), mean, (SD, min-max) (N=913)	68.5 (2.6, 52.0-82.3)	68.6 (2.7, 62,3-77.0)	68.5 (2.7, 52.0-82.7)

E2 a Results of univariate analysis for dry skin as dependent variable presented as complete case analysis showing N (%) of individuals included in the analysis with OR (CI 95%) and p-value.

Pregnancy variables		N (%) of 1150 included in analysis (complete cases for dry skin as outcome)	OR (CI 95%)	p-value
Maternal age (years)	Q1 (21 – 29)	1150 (100%)	Ref.	
	Q2 (30 – 32)		1.20 (0.86-1.65)	0.28
	Q3 (33 – 35)		1.66 (1.17-2.35)	0.004
	Q4 (>35)		1.81 (1.27-2.56)	0.001
Paternal age (years)	Q1 (21 – 30)	983 (85.5%)	Ref.	
	Q2 (31 – 33)		1.55 (1.06-2.26)	0.024
	Q3 (34 – 37)		1.53 (1.06-2.20)	0.023
	Q4 (> 37)		2.04 (1.40-2.97)	<0.0001
Education mother, > 4 years of University		1040 (90.4%)	1.30 (1.01-1.67)	0.039
Education co-parent, > 4 years of University		1001 (87%)	1.06 (0.82-1.36)	0.649
Family income	Low	1032 (89.7%)	Ref.	
	Middle		1.17 (0.82-1.65)	0.388)
	High		1.91 (1.17-3.11)	0.010
BMI, mother at 18 weeks of pregnancy		1132 (98.4%)	1.01 (0.98-1.04)	0.641
≥ 1 previous parity		1046 (91%)	1.25 (0.97-1.61)	0.082
Allergic disease mother		1046 (91%)	1.32 (1.02-1.70)	0.035
Allergic disease father		1023 (89%)	0.93 (0.72-1.19)	0.549
Atopic dermatitis mother, doctor diagnosed		1046 (91%)	1.16 (0.86-1.58)	0.334
Atopic dermatitis father, doctor diagnosed		954 (83%)	0.92 (0.62-1.37)	0.695
Asthma mother, doctor diagnosed		1046 (91%)	0.93 (0.67-1.28)	0.638
Asthma father, doctor diagnosed		1014 (88.2%)	0.83 (0.58-1.18)	0.291
Allergic rhinitis mother, doctor diagnosed		952 (82.8%)	1.48 (1.08-2.02)	0.014
Allergic rhinitis father, doctor diagnosed		957 (83.2%)	1.16 (0.86-1.56)	0.342
Food allergy mother, doctor diagnosed		975 (84.8%)	1.07 (0.74-1.54)	0.724
Food allergy father, doctor diagnosed		990 (86.1%)	1.20 (0.76-1.86)	0.411
Alcohol intake		914 (79.5%)	1.33 (0.78-2.27)	
Smoking		1128 (98.1%)	0.71 (0.40-1.24)	0.228
Snus use		1128 (98.1%)	0.84 (0.53-1.35)	0.478
Rural living		1046 (91%)	0.89 (0.57-1.37)	0.592
Exposure to humidity/mould		984 (85.6%)	1.16 (0.80-1.68)	0.430
Pets (no pets as ref.)		1046 (91%)		
Cat, no dog			0.56 (0.36-0.87)	0.01
Dog, no cat			0.89 (0.61-1.30)	0.544
Cat and dog			1.12 (0.40-3.11)	0.827
Pets except cat and dog			0.90 (0.37-2.15)	0.807
Caesarean section (vaginal as ref.)	Elective	1137 (98.9%)	1.29 (0.76-2.20)	0.344
	Acute		0.90 (0.61-1.34)	0.903
Birth GA (weeks)	Q1 (35.00 – 38.20)	1088 (94.6%)	Ref.	
	Q2 (38.21 – 39.50)		1.87 (1.33-2.63)	<0.0001
	Q3 (39.51 – 40.50)		2.50 (1.75-3.60)	<0.0001
	Q4 (> 40.50)		1.84 (1.32-2.60)	<0.0001
Female sex		1146 (99.7%)	0.89 (0.70-1.13)	0.338
Birth weight (kg)	Q1 (1.50 – 3.30)	1099 (95.6%)	Ref.	
	Q2 (3.31 – 3.60)		1.22 (0.87-1.71)	0.255
	Q3 (3.61 – 3.90)		1.28 (0.91-1.79)	0.159
	Q4 (> 3.90)		1.65 (1.17-2.33)	0.005
Born during winter season (October – March)		1146 (99.7%)	1.28 (1.01-1.63)	0.040

E2 b Results of univariate analysis for high TEWL as dependent variable presented as complete case analysis showing N (%) of individuals included in the analysis with OR (CI 95%) and p-value.

Pregnancy variables		N (%) of 1033 included in analysis (complete cases for high TEWL as outcome)	OR (CI 95%)	p-value
Maternal age (years)	Q1 (21 – 29)	1024 (99.1)	Ref.	
	Q2 (30 – 32)		1.14 (0.68-1.90)	0.621
	Q3 (33 – 35)		1.09 (0.63-1.86)	0.766
	Q4 (>35)		1.02 (0.59-1.75)	0.958
Paternal age (years)	Q1 (21 – 30)	876 (84.8%)	Ref.	
	Q2 (31 – 33)		0.78 (0.43-1.42)	0.415
	Q3 (34 – 37)		0.73 (0.41-1.30)	0.290
	Q4 (> 37)		0.97 (0.55-1.71)	0.919
Education mother, > 4 years of University		925 (89.5%)	1.15 (0.77-1.71)	0.508
Education co-parent, > 4 years of University		892 (86.4%)	1.03 (0.69-1.52)	0.900
Family income	Low	919 (89.0%)	Ref.	
	Middle		0.90 (0.51-1.57)	0.701
	High		1.45 (0.72-2.93)	0.298
BMI, mother at 18 weeks of pregnancy		1007 (97.5%)	1.02 (0.97-1.07)	0.392
≥ 1 previous parity		931 (90.1%)	1.09 (0.73-1.61)	0.683
Allergic disease mother		931 (90.1%)	1.88 (1.20-2.94)	0.006
Allergic disease father		907 (87.8%)	1.25 (0.85-1.84)	0.260
Atopic dermatitis mother, doctor diagnosed		931 (90.1%)	1.58 (1.01-2.47)	0.046
Atopic dermatitis father, doctor diagnosed		840 (81.3%)	1.41 (0.81-2.45)	0.221
Asthma mother, doctor diagnosed		931 (90.1%)	1.79 (1.14-2.82)	0.012
Asthma father, doctor diagnosed		899 (87%)	0.77 (0.43-1.40)	0.391
Allergic rhinitis mother, doctor diagnosed		853 (82.6%)	1.24 (0.77-1.99)	0.372
Allergic rhinitis father, doctor diagnosed		849 (82.2%)	1.40 (0.91-2.15)	0.131
Food allergy mother, doctor diagnosed		866 (83.8%)	1.67 (0.99-2.81)	0.055
Food allergy father, doctor diagnosed		876 (84.8%)	0.78 (0.38-1.61)	0.504
Alcohol intake		811 (78.5%)	1.55 (0.76-3.18)	0.231
Smoking		1004 (97.2%)	1.28 (0.56-2.92)	0.564
Snus use		1004 (97.2%)	1.17 (0.58-2.36)	0.653
Rural living		931 (90.1%)	1.27 (0.65-2.49)	0.483
Exposure to humidity/mould		874 (84.6%)	1.00 (0.56-1.78)	0.986
Pets (no pets as ref.)		931 (90.1%)		
Cat, no dog			0.96 (0.46-1.99)	0.911
Dog, no cat			1.40 (0.80-2.47)	0.240
Cat and dog			1.05 (0.24-4.70)	0.949
Pets except cat and dog			1.23 (0.35-4.25)	0.749
Caesarean section (vaginal as ref.)	Elective	1014 (98.2%)	1.12 (0.52-2.44)	0.768
	Acute		0.99 (0.53-1.82)	0.965
Birth GA (weeks)	Q1 (35.00 – 38.20)	969 (93.8%)	Ref.	
	Q2 (38.21 – 39.50)		1.05 (0.60-1.83)	0.868
	Q3 (39.51 – 40.50)		1.20 (0.69-2.09)	0.524
	Q4 (> 40.50)		1.24 (0.72-2.11)	0.438
Female sex		1020 (98.7%)	0.64 (0.44-0.94)	0.021
Birth weight (kg)	Q1 (1.50 – 3.30)	979 (94.8)	Ref.	
	Q2 (3.31 – 3.60)		0.92 (0.52-1.63)	0.771
	Q3 (3.61 – 3.90)		1.35 (0.79-2.30)	0.268
	Q4 (> 3.90)		1.54 (0.92-2.59)	0.103
Born during winter season (October – March)		1020 (98.7%)	1.90 (1.27-2.82)	0.002

E2 c Results of univariate analysis for eczema as dependent variable presented as complete case analysis showing N (%) of individuals included in the analysis with OR (CI 95%) and p-value.

Pregnancy variables		N (%) of 1150 included in analysis (complete cases for AD as outcome)	OR (CI 95%)	p-value
Maternal age (years)	Q1 (21 – 29)	1150 (100%)	Ref.	
	Q2 (30 – 32)		1.07 (0.63-1.85)	0.796
	Q3 (33 – 35)		1.62 (0.95-2.75)	0.074
	Q4 (>35)		1.80 (1.07-3.04)	0.028
Paternal age (years)	Q1 (21 – 30)	983 (85.5%)	Ref.	
	Q2 (31 – 33)		0.78 (0.42-1.47)	0.445
	Q3 (34 – 37)		1.42 (0.82-2.47)	0.207
	Q4 (> 37)		1.25 (0.71-2.20)	0.448
Education mother, > 4 years of University		1040 (90.4%)	0.92 (0.64-1.34)	0.673
Education co-parent, > 4 years of University		1001 (87.0%)	0.91 (0.62-1.32)	0.622
Family income	Low	1032 (89.7%)	Ref.	
	Middle		1.06 (0.61-1.84)	0.831
	High		1.66 (0.84-3.28)	0.145
BMI, mother at 18 weeks of pregnancy (continuous)		1116 (97.0%)	1.04 (0.00-1.09)	0.117
BMI, mother normal (BMI 18-24.9)			Ref.	
BMI, mother overweight (BMI 25-29.9)			1.23 (0.83-1.81)	0.307
BMI, mother obese (BMI ≥ 30)			1.25 (0.68-2.29)	0.483
≥ 1 previous parity		1046 (91%)	1.84 (1.27-2.67)	0.001
Allergic disease mother		1046 (91%)	1.57 (1.04-2.36)	0.032
Allergic disease father		1023 (89%)	1.46 (1.01-2.13)	0.046
Atopic dermatitis mother, doctor diagnosed		1046 (91%)	1.31 (0.85-2.02)	0.214
Atopic dermatitis father, doctor diagnosed		954 (83%)	1.75 (1.05-2.91)	0.032
Asthma mother, doctor diagnosed		1046 (91%)	1.06 (0.66-1.70)	0.818
Asthma father, doctor diagnosed		1014 (88.2%)	1.04 (0.62-1.75)	0.885
Allergic rhinitis mother, doctor diagnosed		952 (82.8%)	1.15 (0.73-1.80)	0.549
Allergic rhinitis father, doctor diagnosed		957 (83.2%)	1.34 (0.88-2.04)	0.174
Food allergy mother, doctor diagnosed		975 (84.8%)	0.87 (0.48-1.57)	0.643
Food allergy father, doctor diagnosed		990 (86.1%)	1.08 (0.57-2.04)	0.815
Alcohol intake		914 (79.5%)	1.79 (0.94-3.4)	0.076
Smoking		1128 (98.1%)	1.32 (0.61-2.87)	0.483
Snus use		1128 (98.1%)	0.474 (0.10-1.20)	0.114
Rural living		1046 (91%)	0.58 (0.26-1.28)	0.174
Exposure to humidity/mould		984 (95.6%)	0.92 (0.53-1.61)	0.780
Pets (no pets as ref.)		1046 (91%)		
Cat, no dog			1.07 (0.56-2.04)	0.687
Dog, no cat			0.68 (0.36-1.31)	0.254
Cat and dog			0.99 (0.22-4.44)	0.994
Pets except cat and dog			1.64 (0.54-4.97)	0.383
Caesarean section (vaginal as ref.)	Elective	1137 (98.9%)	1.67 (0.86-3.21)	0.128
	Acute		1.12 (0.63-1.99)	0.710
Birth GA (weeks)	Q1 (35.00 – 38.20)	1088 (94.6%)	Ref.	
	Q2 (38.21 – 39.50)		1.16 (0.69-1.94)	0.585
	Q3 (39.51 – 40.50)		1.16 (0.68-1.98)	0.590
	Q4 (> 40.50)		1.34 (0.81-2.22)	0.259
Female sex		1146 (99.7%)	0.75 (0.52-1.01)	0.107
Birth weight (kg)	Q1 (1.50 – 3.30)	1099 (95.6%)	Ref.	
	Q2 (3.31 – 3.60)		1.18 (0.68-2.03)	0.559
	Q3 (3.61 – 3.90)		1.34 (0.78-2.27)	0.280
	Q4 (> 3.90)		1.89 (1.14-3.13)	0.014
Born during winter season (October – March)		1146 (99.7%)	1.26 (0.88-1.80)	0.201

Table E3
Multivariate complete case logistic regression, where dependent variables were Dry skin (Table E3a), High TEWL (TEWL > 90th percentile (11.3 g/m^2/h)) (Table E3b) and 'Eczema' (Table E3c) in 1150 3 month-old infants.

GA: Gestational age
OR: Odds Ratio
CI: Confidence interval
Q: Quartile

E3a *Dry skin*

Pregnancy variables	**N=879 OR (95 % CI)**	**P-value**
Birth GA (weeks)		
Q1 (35.00 – 38.20)		Ref.
Q2 (38.21 – 39.50)	1.78 (1.20-2.67)	0.005
Q3 (39.51 – 40.50)	2.46 (1.60-3.79)	<0.0001
Q4 (> 40.50)	1.70 (1.12-2.58)	0.013
Birth weight (kg)		
Q1 (1.50 – 3.30)		Ref.
Q2 (3.31 – 3.60)	1.03 (0.69-1.53)	0.883
Q3 (3.61 – 3.90)	1.00 (0.66-1.52)	0.987
Q4 (> 3.90)	1.36 (0.89-2.08)	0.163
Multipara	1.02 (0.75-1.41)	0.882
Domestic cat exposure	0.554 (0.33-0.92)	0.023
Maternal age (years)		
Q1 (21 – 29		Ref.
Q2 (30 – 32)	0.84 (0.61-1.44)	0.769
Q3 (33 – 35)	1.36 (0.83-2.22)	0.747
Q4 (>35)	1.10 (0.63-1.90)	0.747
Paternal age (years)		
Q1 (21 – 30)		Ref.
Q2 (31 – 33)	1.63 (1.03-2.59)	0.037
Q3 (34 – 37)	1.45 (0.90-2.31)	0.124
Q4 (> 37)	1.96 (1.16-3.30)	0.012
Maternal allergic disease	1.28 (0.95-1.712)	0.106
Maternal education > 4 years University	1.10 (0.81-1.49)	0.565
Family income		
Low		Ref.
Middle	0.93 (0.61-1.44)	0.754
High	1.34 (0.73-2.46)	0.351
Born during winter season	1.29 (0.97-1.72)	0.076

E3b *High TEWL*

Pregnancy variables	**N=888 OR (95 % CI)**	**P-value**
Female sex	0.61 (0.40-0.93)	0.022
Birth weight (kg)		
Q1 (1.50 – 3.30)	Ref.	
Q2 (3.31 – 3.60)	0.95 (0.52-1.76)	0.879
Q3 (3.61 – 3.90)	1.26 (0.70-2.27)	0.445
Q4 (> 3.90)	1.33 (0.74-2.38)	0.337
Maternal any allergic disease	1.80 (1.08-3.01)	0.025
Maternal atopic dermatitis	1.29 (0.78-2.12)	0.321
Maternal asthma	1.34 (0.18-2.23)	0.256
Born during winter season	2.02 (1.31-3.14)	0.002

E3c *Eczema*

Pregnancy variables	**N=893 OR (95%CI)**	**p-value**
Sex (females)	0.83 (0.54-1.26)	0.380
Birth weight (kg)		
Q1 (1.50 – 3.30)		Ref.
Q2 (3.31 – 3.60)	1.17 (0.62-2.22)	0.632
Q3 (3.61 – 3.90)	1.50 (0.80-2.78)	0.203
Q4 (> 3.90)	1.77 (0.97-3.25)	0.065
Elective caesarean section	2.50 (1.19-5.25)	0.016
Multiparity	1.63 (1.03-2.57)	0.037
Maternal age (years)		
Q1 (21 – 29)		Ref.
Q2 (30 – 32)	0.90 (0.47-1.74)	0.757
Q3 (33 – 35)	1.41 (0.73-2.75)	0.311
Q4 (>35)	1.65 (0.85-3.22)	0.143
Maternal allergic disease	1.61 (1.02-2.55)	0.041
Paternal allergic disease	1.41 (0.93-2.14)	0.105
Snus during pregnancy	0.43 (0.15-1.24)	0.120
Rural living	0.48 (0.20-1.15)	0.101
Family income		
Low		Ref.
Middle	0.91 (0.47-1.75)	0.777
High	1.14 (0.51-2.54)	0.755