Prevalence of atopic dermatitis in infants by domestic water hardness and season of birth: Cohort study

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Background: Atopic dermatitis (AD) appears to be more common in regions with hard domestic water and in children with a fall/winter birth. However, it is unknown whether a synergistic effect exists.
Objective: We sought to evaluate the association between domestic water hardness and season of birth, respectively, with onset of AD within the first 18 months of life in a large Danish birth cohort.
Methods: Of children from the Danish National Birth Cohort, 52,950 were included. History of physician-diagnosed AD and population characteristics were obtained from interviews. Birth data were obtained from the Civil Registration System, and domestic water hardness data were obtained from the Geological Survey of Denmark and Greenland. The relative prevalence (RP) of AD was calculated by using log-linear binomial regression.
Results: The prevalence of AD was 15.0% (7,942/52,950). The RP of AD was 5% (RP_{trend}, 1.05; 95% CI, 1.03-1.07) higher for each 5° increase in domestic water hardness (range, 6.60-35.90 German degrees of hardness [118-641 mg/L]). Although the RP of AD was higher in children with a fall (RP, 1.24; 95% CI, 1.17-1.31) or winter (RP, 1.18; 95% CI, 1.11-1.25) birth, no significant interaction was observed with domestic water hardness. The population attributable risk of hard domestic water on AD was 2%.
Conclusion: We observed that early exposure to hard domestic water and a fall/winter birth was associated with an increase in the relative prevalence of AD within the first 18 months of life. Although the 2 exposures did not interact synergistically, a dose-response relationship was observed between domestic water hardness and AD. (J Allergy Clin Immunol 2017;139:1568-74.)

Key words: *Atopic dermatitis, birth cohort, climate, risk factors, season of birth, water hardness*

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Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition characterized by xerotic and pruritic skin, as well as dermatitis in typical anatomic sites. The etiopathogenesis of AD is incompletely understood, but both primary skin barrier abnormality and immune dysregulation can result in downstream pathogenic events.[1] In support of the pertinent role of a competent skin barrier against the development of AD, loss-of-function mutations in the filaggrin gene *(FLG)* have been identified as the hitherto strongest genetic risk factor for AD and, in particular, for early-onset AD.[2] Moreover, skin barrier impairment in newborns appears to predict onset of AD at 1 year of age,[3] and pilot studies have shown that barrier restoration with emollients in newborns reduces the risk of AD.[4-6]

In addition to genetic factors, exogenous skin stressors can compromise skin barrier function and increase the risk of AD. For example, climatic conditions, such as low ambient humidity, low temperature, and a reduction in UV irradiation, negatively affect the skin barrier and increase the risk of AD.[7-9] Accordingly, a significantly higher prevalence of AD has been found in children born in the fall and winter and in children living in parts of the United States with such climatic conditions.[7,10-13] In Denmark the average temperature during winter is 1.6°C, the ambient humidity is low, and there are few hours of daylight. The summer climate is mild (average temperature, 16.4°C), with slightly higher ambient humidity and longer sunny days.

Water is a known skin irritant,[14] and so-called hard water, which is characterized by a high calcium carbonate content, might

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J.P.T. and K.A.E. are financially supported by an unrestricted grant from the Lundbeck Foundation. P.B. is supported by an Oak Foundation fellowship. The Danish National Research Foundation has established the Danish Epidemiology Science Centre, which initiated and created the Danish National Birth Cohort (DNBC); furthermore, the cohort is a result of a major grant from this foundation. Additional support for the DNBC is obtained from the Pharmacy Foundation, the Egmont Foundation, the March Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Foundation.

Disclosure of potential conflict of interest: K. A. Engebretsen's institution has received a grant from the Lundbeck Foundation. P. Bager's institution received money from the OAK foundation. L. Skov's institution has received financial for consultancy fees. M. Melbye is employed by the Ministry of Health. J. P. Thyssen's institution has received a grant from the Lundbeck Foundation, and he has received consultancy fees from Roche, payment for lectures from Meda and Galderma, and royalties from the Cobalt Spot Test. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication May 17, 2016; revised November 2, 2016; accepted for publication November 17, 2016.

Available online December 23, 2016.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2016.11.021

Abbreviations used
AD: Atopic dermatitis
°dH: German degrees of hardness
DNBC: Danish National Birth Cohort
GEUS: Geological Survey of Denmark and Greenland
RP: Relative prevalence
UK: United Kingdom

particularly impair skin barrier functions.[15] Accordingly, some, but not all, epidemiologic studies have found a higher prevalence of AD in regions with hard domestic water when compared with regions with soft water.[16-20] Notably, a recent study from the United Kingdom (UK) showed an association between domestic water hardness and AD in 3-month-old infants,[21] whereas most other studies have been conducted in older children. The domestic water hardness varies greatly around the world. The mineral content of drinking water in Asia is generally low (between 2 and 80 mg/L), whereas in the United States, the UK, and also Australia, the domestic water hardness ranges from soft (0-60 mg/L) to very hard (≥181 mg/L).[22]

Large and solid epidemiologic studies are needed to further investigate the association between domestic water hardness and AD and particularly studies that examine the effect on infant AD. Therefore we used the uniquely wide range of domestic water hardness in Denmark to evaluate the possible association with AD within the first 18 months of life in a large nationwide birth cohort. We also examined whether a synergistic effect of both being exposed to hard domestic water and having a fall/winter birth exists in a country with relatively cold winters. Finally, we calculated the population attributable risk of AD in children exposed to hard domestic water.

METHODS

Danish National Birth Cohort study

The Danish National Birth Cohort study (DNBC) is an ongoing study with the aim to investigate how exposures over the life course, including early life, affect health and disease susceptibility later in life (www.dnbc.dk).[23] Between 1996 and 2002, the DNBC study enrolled pregnant women from all of Denmark, who then were invited to participate in telephone interviews in the 12th and 30th weeks of their pregnancies and when offspring were aged 6 and 18 months.[24] The women were recruited by their general practitioner at the first pregnancy visit around weeks 6 to 12. In total, the study enrolled 100,329 pregnancies by 91,326 women, resulting in 96,838 liveborn children; 70,296 completed the interview at 6 months and 66,764 completed the interview at 18 months of age. As part of the study, information about residence at birth, including municipality code, and date of birth was obtained from the Civil Registration System for all liveborn children.[25]

Study population

The study population consisted of 55,092 liveborn singleton children in the DNBC whose mothers completed the interview at 6 and 18 months of age with information on AD (outcome of interest). We excluded children with missing information on maternal socio-occupational class and history of AD based on the first interview, respectively (1,973 mothers did not participate in the interview, and 169 had missing information); the remaining 52,950 (96%) children had complete information on outcome, exposures, and covariates and were thus eligible for inclusion in the study.

Exposures

Domestic water hardness. In Denmark the range between soft and hard domestic water, which is extracted from ground reservoirs, is relatively large when compared with that in other nations. This is explained by a unique geology, which is visualized as the north-south line ("the main stationary line"), where the last ice age glacier stopped on its way from the northeast. Thus very soft ground water from quartz sand reservoirs is found in the western parts of Denmark, whereas the ground water is very hard in the eastern parts because of thick layers of glacial till with calcium (Fig 1).[26]

Information about domestic water hardness in Denmark was obtained from the Geological Survey of Denmark and Greenland (GEUS; www.geus.dk). The GEUS is a governmental institution that performs and coordinates measurements of all ground water wells used for domestic water in Denmark. Domestic water hardness was measured in German degrees of hardness (°dH) and provided as a mean value (2 decimals) for all the waterworks within each municipality (1°dH = 17.85 mg/L). The cutoff points were provided by the GEUS and historically been chosen after advice from their senior hydrogeologist. Using the municipality code as key, we identified the mean hardness of the domestic water used in the municipality where each child in the cohort was born.

Time of birth

Time of birth (month and season) was derived from the birth date obtained from the Civil Registration System in Denmark.

Outcome

A diagnosis of AD was based on a positive response to the question "Has a doctor ever told you that your child has atopic dermatitis?," which appeared in the last 2 interviews (child aged 6 and 18 months). If the answer was confirmative in one of these interviews, the child was registered as having AD.

Covariates

Covariates chosen to describe the study population were sex, history of maternal AD, type of municipality, maternal socio-occupational class, and age at the last interview with information on AD. A history of maternal AD was assessed in the interview at pregnancy week 12, during which the mothers were asked the following: "Have you ever had a skin disease?" If the answer was confirmative, mothers were asked the following: "Which skin diseases have you had?" Danish municipalities have previously been divided into 4 categories according to the degree of rurality (ie, urban, intermediate, rural, and remote. Indicators included, amongst others, the following: inhabitants per square kilometer, distance to the nearest highway, age composition of inhabitants, educational level, economy, and the importance of agriculture.[27] Maternal socio-occupational class was based on the mother's current or most recent occupation, as well as type of education, and was then divided into 5 categories accordingly: long higher education or leaders in large companies, middle-long higher education or leaders in small companies, short higher education/vocational education or undereducation, unskilled/other work or unemployment benefits, and supported by the state. The child's age at the last interview was calculated from the date of interview and birth.

Statistical analyses

The association between the prevalence of AD, domestic water hardness, and season of birth was evaluated by the relative prevalence (RP) estimated with log-linear binomial regression in PROC GENMOD in SAS software, version 9.4 (SAS Institute, Cary, NC). The trend estimate for domestic water hardness was estimated by treating water hardness as a continuous variable. For time of birth, the RP for AD was calculated by 4 seasons, with spring as the reference.

RPs were presented as crude estimates; however, in multivariable analyses we also adjusted for covariates, as categorized in Table I. The interaction between water hardness and season of birth was tested by including a multiplicative interaction term. RPs stratified by age at onset and P values for heterogeneity (P_{het}) were estimated with log-linear polytomous regression