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Domestic Dog Exposure at birth reduces the Incidence of Atopic Dermatitis

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Short title: Dog protects against atopic dermatitis

Abbreviations:

AD = atopic dermatitis

COPSAC₂₀₀₀ = COpenhagen Prospective Studies on Asthma in Childhood₂₀₀₀

COPSAC₂₀₁₀ = COpenhagen Prospective Studies on Asthma in Childhood₂₀₁₀

FLG=filaggrin gene

HR=hazard ratio

TROLS= troublesome lung symptoms

Ig=immunoglobulin

slg=specific immunoglobulin

ABSTRACT

Background

While the etiopathogenesis of atopic dermatitis is complex and poorly understood, neonatal exposures are important for disease occurrence. However, the effect of dog exposure on the risk of atopic dermatitis is unresolved.

Objective

We investigated whether domestic dog exposure affected the risk of atopic dermatitis in children during the first 3 years of life.

Methods

Copenhagen prospective studies on asthma in childhood (COPSAC) are ongoing prospective clinical birth cohort studies. Data from 411 children born to mothers with asthma (COPSAC₂₀₀₀), and 700 unselected children (COPSAC₂₀₁₀) were analyzed following the same protocols at the same research site. Atopic dermatitis was diagnosed prospectively according to the Hanifin-Rajka criteria. Parental history of asthma, eczema or rhinitis was defined by self-reported physician diagnosis. In COPSAC₂₀₀₀, maternal specific serum IgE against 8 inhalant allergens was sampled after the children's birth and at pregnancy week 24 in the COPSAC₂₀₁₀ cohort. Associations between dog exposure and atopic dermatitis were analyzed by Cox' proportional hazard regression models and adjusted for lifestyle confounders.

Results

In COPSAC₂₀₀₀ and COPSAC₂₀₁₀ cohorts, the risk of atopic dermatitis was significantly lower in children with domestic dog exposure, (_{adjusted}HR=0.46 [0.25-0.87], p=0.02) and (_{adjusted}HR=0.58 [0.36-0.93], p=0.03), respectively. The risk of atopic dermatitis decreased in a dose-dependent manner with increasing number of dogs (_{adjusted}HR =0.58 [0.38-0.89], p=0.01) in COPSAC₂₀₁₀. The protective effect was restricted to children born by mothers with atopic disease in the unselected COPSAC₂₀₁₀ cohort; (_{adjusted}HR =0.39 [0.19-0.82], p=0.01), since no effect was observed in children born by mothers without atopic disease; (_{adjusted}HR =0.92 [0.49-1.73], p=0.79). Paternal atopic status did not affect the risk of atopic dermatitis. We found no significant interaction between the CD14 T/T genotype and domestic dog exposure in either cohort, COPSAC₂₀₀₀, p=0.36, and COPSAC₂₀₁₀ cohort, p=0.42.

Conclusion

Neonatal domestic dog exposure was associated with a strongly reduced risk of atopic dermatitis in two independent birth cohorts and in a dose-dependent manner. While the mechanisms involved are unclear, our findings raise the question whether *in utero* exposures may affect the risk of atopic dermatitis and emphasize the importance of the early environment for disease trajectory.

Key Messages:

- The effect of dog exposure on the risk of atopic dermatitis is unresolved.
- We found that domestic dog exposure at home at birth was associated with a dose-related reduced risk of AD in early life in two independent cohorts. The protective effect was restricted to children born to mothers with atopic disease in the COPSAC₂₀₁₀ cohort.
- Our findings emphasize the importance of the perinatal environment for disease trajectory, and future studies should further study the mechanism of this effect, which may involve an interplay between the microbiome and innate immune system.

Keywords, MeSH:

Atopic Dermatitis

Dog

Perinatal exposures

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin condition that affects up to 25% of pediatric populations.(1–4) AD has a strong negative impact on quality of life in affected children and their families.(5) Besides the well-established relationship with asthma and rhinitis, AD has recently been associated with cardiovascular (6,7) and neuropsychiatric comorbidities.(8) While it is a common misconception that most children will outgrow their AD, a recent prospective study showed that by age 20 years, about 50% of patients with childhood AD were still symptomatic.(9)

The etiopathogenesis of AD is multifactorial and complex. Heritability estimates for AD have been estimated to reach 71-84% emphasizing the strong genetic component. (10) While identification of causative environmental factors has proven to be difficult with conflicting study outcomes,(11) exposure to domesticated furry pets has repeatedly been proposed to influence the incidence of AD.(12) Hence, cat ownership strongly increased the risk of AD in Danish and British children with filaggrin gene (*FLG*) mutations; a finding that has since been confirmed in other populations.(13,14) However, previous studies have provided conflicting results on the possible effect of dog exposure on the risk of AD although many have favored a protective effect,(12,15–19). Interestingly, one study showed that variations in the CD14 gene, encoding a surface antigen that mediates the innate immune response to bacterial lipopolysaccharide, in combination with dog exposure significantly reduced the incidence of AD.(20)

In the present study, we analyzed the longitudinal effect of domestic dog exposure on the development of AD in two independent prospective birth cohorts. We further explored whether parental atopic disease, number of dogs, as well as infant CD14 and *FLG* mutation genotypes, could affect this relationship.

METHODS

Data from two independent birth cohorts were analyzed. COPSAC₂₀₀₀ is a high-risk cohort of 411 children born to mothers with asthma. COPSAC₂₀₁₀ is a mother-child cohort of 700 children born to an unselected group of mothers. The recruitment strategies and characteristics of the cohorts have previously been described in detail.(21,22) Participants were followed closely at the central research clinic with scheduled biannual visits and additional visits upon acute onset of clinical symptoms related to the airways or skin. At every visit, a full physical examination was performed and families were interviewed using structured questions and closed response categories focusing on symptoms from the child's lung and skin, use of medication and healthcare, lifestyle factors, and home environment exposures. The pediatricians at the COPSAC clinics were solely responsible for diagnosis and treatment of all respiratory, allergy and skin-related symptoms according to predefined validated algorithms. Data validation and quality control followed the guidelines for good clinical practice. Both studies were performed in accordance with the Declaration of Helsinki and approved by the Copenhagen Ethics Committee (KF01-289/96 + H-B-2008-093) and the Danish Data Protection Agency (J.nr. 2015-41-3696).(21,22)

Domestic exposure to pets

Information about domestic dog exposure was obtained by personal interviews conducted during clinical visits (COPSAC₂₀₀₀ at 1 month visit and COPSAC₂₀₁₀ at 1 week visit), and was defined as a dog living in the home at birth. A similar protocol applied in both cohorts, and information about domestic cat exposure was also obtained in a similar way. (21,22) The number of dogs in the COPSAC₂₀₁₀ cohort was divided into three groups: (i) no dogs, (ii) one dog and (iii) two or more dogs.

Atopic dermatitis

AD was diagnosed according to the criteria of Hanifin and Rajka.(23) A diagnosis of AD required the presence of 3 of 4 major criteria and at least 3 of 23 minor signs. The following 4 minor signs were excluded: keratoconus and anterior sub-capsular cataracts, delayed blanch and impaired cell-mediated immunity.

Daily diary cards

In the COPSAC₂₀₁₀ cohort, parents kept a daily diary of children's clinical symptoms, including their skin condition. The diary cards were reviewed by the COPSAC physicians at scheduled visits as well as during visits for acute skin manifestations to confirm manifestations of AD.(22) A diary was defined as valid if more than 90% of the days were completed. The numbers of days with active AD as well as days with topical anti-inflammatory product use were analyzed.

Asthma

A strict predefined algorithm was used to diagnose asthma. This included 1) recurrent troublesome lung symptoms 2) symptoms typical of asthma 3) need of intermittent rescue use of inhaled β 2-agonist and 4) response to a 3-month course of inhaled corticosteroids of 400 μ g/d and relapse when stopping treatment.(24)

Sensitization in children

Specific serum immunoglobulin (Ig) E levels were determined at 6 and 18 months of age by ImmunoCAP, Phadiatop Infant TM (Pharmacia Diagnostics AB, Uppsala, Sweden). IgE against 8 inhalant allergens (dog, cat, horse, birch, timothy grass, mugwort, *D.Pteronyssinus*, and molds), 6 food allergens (milk, egg, wheat flour, soybean, cod and peanut), and fresh cow's milk and pasteurized hen's egg were measured. Values ≥ 0.35 kU/ml were considered positive.

Skin prick testing (SPT) was performed using standard allergen extracts (Soluprick[®] SQ; ALK-Abello, Hørsholm, Denmark) against the same panel of inhalant and food allergens as listed above for IgE. A positive reaction was defined as a wheal diameter ≥ 2 mm larger than the negative control at 6 and 18 months.

Filaggrin gene mutations

Genotyping for R501X, 2282del4, R2447X and S3247X loss-of-function mutations in *FLG* was performed as previously described.(25) Children with at least one gene mutation were classified as being *FLG* mutation carriers.

CD14 genotype

Multiple single-nucleotide polymorphisms (SNPs) were genotyped genome-wide using the high throughput Illumina HumanOmniExpressExome bead chip platform (Illumina, Inc., San Diego, CA, USA) at AROS Applied Biotechnology AS, Aarhus, Denmark.

Genotyping quality control included removal of gender mismatches, duplicates, ethnic outliers, and Hardy-Weinberg equilibrium ($p > 10^{-6}$) outliers. A genotyping call rate of at least 95% was required. Correct familial relations were verified by Mendel error rates and identity-by-descent analyses. All quality control was performed using PLINK software.(26) The HumanOmniExpressExome chip was imputed to the 1000 genomes phase 3 imputation panels (CEU individuals) using Mach 1.0, Markov Chain Haplotyping, and IMPUTE2, including imputation to CD14 genotype, rs2569190, with an imputation certainty of 0.99.

Parental atopy status

Atopic disease was registered if the parents reported a history of asthma, eczema or allergic rhinitis diagnosed by a physician. In the COPSAC₂₀₀₀ cohort, serum sIgE levels in the parents were determined in blood samples taken after the children's birth. In the COPSAC₂₀₁₀ cohort, parental levels of sIgE were determined in blood samples drawn at week 24 of pregnancy and all samples were analyzed by the screening method (ImmunoCAP, PhadiatopTM, Pharmacia Diagnostics AB, Uppsala Sweden).(27) sIgE against 7 inhalant allergens (dog, cat, birch, timothy grass, mugwort, *D.Pteronyssinus*, and molds) was analyzed. Parental sensitization was defined as sIgE above 0.35 kU/ml for both sensitization to at least one allergen and also for sensitization to one specific allergen.

Statistical analyses

The Chi-square test, student's t-test and Wilcoxon rank-sum test were used to test for simple associations in the baseline characteristics of the cohorts. Associations between dog exposure and AD were analyzed by Cox' proportional hazard regression models and adjusted for the following lifestyle confounders that differed significantly between the groups in crude data analysis: maternal tobacco smoking, maternal educational level, and days of exclusive breastfeeding. The dose-dependent analyses for domestic dog and cat exposure at birth were furthermore adjusted for parental allergic sensitization to dogs and cats, respectively. The same model was used to analyze associations between dog exposure and asthma. Associations between the CD14/TT genotype (dominant model) and AD were analyzed by Cox' proportional hazard regression models and adjusted for sex. Poisson regression model analyses were used to evaluate associations between dog exposure and days with clinically active AD and topical corticosteroid use. Results were reported with 95% confidence intervals (CI) and a significance level of 0.05 was used. Missing observations were treated as missing data. The data processing was conducted using SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 162 (45%) children from the high risk COPSAC₂₀₀₀ cohort and 174 (25%) children from the unselected COPSAC₂₀₁₀ cohort developed AD during the first 3 years of life. Fifty-five (14%) of COPSAC₂₀₀₀ and 132 (19%) of COPSAC₂₀₁₀ participants reported dog living in the home around birth. In COPSAC₂₀₁₀, 110 (16%) children had only one dog, whereas 22 (3%) children had two or more dogs. No information on number of dogs was available for COPSAC₂₀₀₀. In both cohorts, mothers exposed to domestic dog(s) smoked tobacco more often and had an overall lower educational level

(Table 1). In the COPSAC₂₀₁₀ cohort, they also exclusively breastfed their children fewer days. A similar trend, albeit it was not statistically significant, was observed in the COPSAC₂₀₀₀ cohort. To reduce the risk of confounding, all analyses were therefore adjusted for tobacco smoking, educational level and days of exclusive breastfeeding. We observed no significant difference in the prevalence of sensitization to dog among mothers and fathers with and without domestic dog exposure.

Dog exposure and the risk of atopic dermatitis

Dog exposure was associated with a significantly lower risk of AD in both COPSAC₂₀₀₀ (adjusted HR =0.46 [0.25-0.87], p=0.02) and COPSAC₂₀₁₀ (adjusted HR =0.58 [0.36-0.93], p=0.03) (Figure 1). No children were sensitized to dog before onset of AD in the COPSAC₂₀₀₀ cohort, and only 1 child was sensitized to dog in the COPSAC₂₀₁₀ cohort. Within the unselected COPSAC₂₀₁₀ cohort, the protective effect of domestic dog exposure was restricted to children born to mothers with atopic disease i.e. a physician diagnosis of asthma, eczema or rhinitis: (adjusted HR =0.39 [0.19-0.82], p=0.01). Hence, in children born to mothers without atopic disease, no significant association between dog exposure and risk of AD was observed: (adjusted HR =0.92 [0.49-1.73], p=0.79) (Figure 2). The risk of AD decreased in a dose-dependent manner with increasing number of dogs (adjusted HR =0.58 [0.38-0.89], p=0.01) in COPSAC₂₀₁₀ (Figure 3). This information was not available in the COPSAC₂₀₀₀ cohort. While maternal sensitization (sIgE≥0.35) increased the risk of AD in the child (adjusted HR =1.36 [1.00-1.84] p=0.05) in COPSAC₂₀₁₀ cohort, the protective effect of domestic dog exposure on the risk of AD was restricted to children born to sensitized mothers; (adjusted HR =0.22 [0.07-0.72], p=0.01). Thus, no significant effect of dog exposure was observed in children of non-sensitized mothers; (adjusted HR =0.77 [0.45-1.31], p=0.34). While the interaction between maternal sensitization and dog exposure was significant p=0.03, no interaction was observed between paternal atopic or sensitization status and the effect of dog exposure on the development of AD in their child. In COPSAC₂₀₀₀, all mothers

had asthma. Here, the effect of dog exposure on AD was independent of maternal sensitization (sensitized, $\text{adjustedHR} = 0.50$ [0.23-1.07], $p=0.07$ and non-sensitized, ($\text{adjustedHR} = 0.41$ [0.16-1.06], $p=0.06$) (Figure 4).

Dog exposure and daily symptoms of atopic dermatitis

In the COPSAC₂₀₁₀ cohort, domestic dog exposure did not reduce the number of total days with clinically active AD ($\text{IRR}=0.76$ [0.44-1.33] $p=0.34$) or the overall use of topical corticosteroids ($\text{IRR}=0.82$ [0.46-1.47] $p=0.50$). Daily symptom registration was not available in the COPSAC₂₀₀₀ cohort.

Filaggrin mutations and the effect of dog exposure

A total of 50 (12%) children in the COPSAC₂₀₀₀ cohort and 72 (10%) in the COPSAC₂₀₁₀ cohort had loss-of-function mutations in *FLG*. Dog exposure did not have an effect on the development of AD in children with *FLG* mutations: COPSAC₂₀₀₀ cohort ($\text{adjustedHR} = 0.15$ [0.02-1.13], $p=0.07$) and COPSAC₂₀₁₀ cohort ($\text{adjustedHR} = 0.78$ [0.26-2.35], $p=0.66$).

CD14 variations and the effect of dog exposure

A trend towards increased risk of AD in children with a CD14 T/T genotype (dominant model) was observed although it was non-significant in both the COPSAC₂₀₀₀ cohort ($\text{adjustedHR} = 1.29$ [0.86-1.93], $p=0.22$) and the COPSAC₂₀₁₀ cohort ($\text{adjustedHR} = 1.36$ [0.94-1.96], $p=0.10$). In both cohort's no significant interaction was found between the CD14 T/T genotype (dominant model) and domestic dog exposure on the development of AD ($\text{adjustedHR} = 1.96$ [0.47-8.20], $p=0.36$ for the COPSAC₂₀₀₀ cohort and ($\text{adjustedHR} = 1.54$ [0.54-4.45], $p=0.42$ for the COPSAC₂₀₁₀ cohort).

Cat exposure and risk of atopic dermatitis

A total of 61 (15%) children from COPSAC₂₀₀₀ and 147 (21%) children from COPSAC₂₀₁₀ had a cat in the home around birth. Domestic cat exposure had no effect on the development of AD by 3 years of age in either of the cohorts: $\text{adjustedHR} = 1.06$ [0.65-1.75], $p=0.81$ in the COPSAC₂₀₀₀ cohort and $\text{adjustedHR} = 0.93$ [0.63-1.39], $p=0.73$ in the COPSAC₂₀₁₀ cohort. Sub-analyses in the COPSAC₂₀₁₀ cohort showed similar results in children born to mothers with or without atopic disease. In addition, the protective effect of dog was independent of cat ownership (data not shown).

Dog exposure and risk of asthma

In both cohorts, no protective effect of domestic dog exposure was seen on the development of asthma in the children by age 3 years: $\text{adjustedHR} = 0.70$ [0.30-1.64], $p=0.41$ in the COPSAC₂₀₀₀ cohort and $\text{adjustedHR} = 0.90$ [0.56-1.42], $p=0.64$ in the unselected COPSAC₂₀₁₀ cohort. Stratification by maternal history of atopic disease or sensitization in the COPSAC₂₀₁₀ cohort did not change the results.

DISCUSSION

Primary findings

Domestic exposure to dog(s) around the time of birth significantly and dose-dependently reduced the risk of AD in children prospectively followed until age 3 years in two independent mother-child cohorts. The protective effect was restricted to children born to mothers with a history of atopic disease, whereas paternal atopic status appeared to be irrelevant. No effect of *FLG* mutations and CD14 genotype was observed.

Strengths and limitations

The main strength of this study is the prospective design of the COPSAC₂₀₀₀ and COPSAC₂₀₁₀ birth cohorts. Children were cared for by the same physicians at planned visits every 6 months, as well as at visits due to acute skin manifestations. The COPSAC physicians used predefined algorithms to diagnose and treat the children. Strict monitoring minimized recall bias and strengthened the diagnosis of AD. Although the COPSAC₂₀₁₀ cohort is an unselected cohort, bias in the prevalence estimate cannot be ruled out as mothers who participated could be more health conscious. This may bias the accuracy of the prevalence estimate, but to a smaller degree the association estimates. Unknown life-style confounders associated with dog ownership could have influenced the study outcomes. Notably, we found no difference in domestic dog exposure and sensitization to dog among the groups of parents who had atopic disease compared to healthy controls suggesting that avoidance behavior was not a major factor in our study. The observed dose-dependent effect of dog exposure also argues against such bias.

Interpretation

A protective effect of domestic dog exposure was restricted to children born to mothers with atopic disease in the COPSAC₂₀₁₀ cohort. Since paternal atopic disease had no influence on the development of AD in the children, the protective effect of domestic dog exposure probably could already have occurred *in utero* in mothers with atopic disease. We have previously shown that neonates born to mothers with a history of atopic disease displayed an altered immune profile in their airway mucosa, whereas no effect was seen from a history of paternal atopic disease, suggesting maternal imprinting *in utero* or perinatally.(28) Moreover, it has previously been suggested that up-regulation of the innate immune system in children exposed to an environment rich in microbial components might decrease the risk of atopic disease(29–31)

. While studies attempting to also correlate genetic variations in toll-like receptors (TLR) and CD14 genes with atopic disease have been conflicting, the collection of studies supports the existence of a gene-environment interaction.(20,31,32) While we found a trend towards an increased risk of AD in carriers of a CD14 T/T genotype, there was no interaction between CD14 T/T genotype and having a dog in the home at birth on the risk of AD.

Presence of dog(s) appear to have a significant effect on domestic bacterial community composition, which becomes more diverse and has a higher relative abundances of canine bacterial taxa.³⁰

Interestingly, a reduction in intestinal microbial diversity during the first month of life has been associated with increased risk of AD and sensitization (34,35) and exposure to a furry pet in pregnant women with atopic sensitization and/or a history of atopic disease can alter the composition of the gut microbiome in the offspring.(36) Also, pregnant women in the COPSAC₂₀₁₀ cohort, who were exposed to a domestic cat or dog had increased vaginal colonization with *Escherichia coli* when compared to controls (37) pointing towards microbial transfer between pet and owner. These observations suggest that the protective effect of domestic dog exposure could be mediated by the microbiome.

We evaluated whether the protective effect of domestic dog exposure could be explained by co-exposure to cat, sensitization to dog, or the presence of *FLG* mutations, but all these analyses were negative in the COPSAC₂₀₁₀ cohort. Also, we evaluated whether dog exposure could affect the clinical course and severity of dermatitis in children with AD but found no effect. The results of previous studies evaluating the potential effect of dog exposure on AD prevalence have been conflicting although in a metaanalyses by Peluchi et al they found a favorable effect of dog exposure on AD.(15–17)

However, most studies have evaluated dog exposure throughout childhood and not included perinatal exposure, or have not stratified for maternal atopic disease. Notably, Ownby et al., found that exposure to two or more dogs or cats in the first year of life reduced the risk of allergic sensitization, while Remes et al., were unable to detect a difference between children exposed to one or two or more dogs on frequent wheeze.(38,39) We found a significant relationship between the number of dogs and the development of AD in the COPSAC₂₀₁₀ cohort suggesting a stronger protective effect with increased dog exposure.

Conclusion

Domestic dog exposure at home at birth was associated with a dose-related reduced risk of AD in early life in two independent cohorts. The protective effect was restricted to children born to mothers with atopic disease in the COPSAC₂₀₁₀ cohort. Our findings emphasize the importance of the perinatal environment for disease trajectory, and future studies should further study the mechanism of this effect, which may involve an interplay between the microbiome and innate immune system.

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None of the authors declare any potential, perceived, or real conflict of interest regarding the content of this manuscript.

We are aware of and comply with recognized codes of good research practice, including the Danish Code of Conduct for Research Integrity. We comply with national and international rules on the safety and rights of patients and healthy subjects, including Good Clinical Practice (GCP) as defined in the EU's Directive on Good Clinical Practice, the International Conference on Harmonisation's (ICH) good clinical practice guidelines and the Helsinki Declaration. We follow national and international rules on the processing of personal data, including the Danish Act on Processing of Personal Data and the practice of the Danish Data Inspectorate. The guarantor of the study is HB, from conception and design to conduct of the study and acquisition of data, data analysis, and interpretation of data. All co-authors have contributed substantially to the analyses and interpretation of the data, and have provided important intellectual input. Sunna Thorsteinsdottir has written the first draft of the manuscript. All authors have agreed that the accuracy and integrity of any part of the work has been appropriately investigated and resolved and all have approved the final version of the manuscript. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

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TABLE

Table 1: Baseline characteristics of the COPSAC₂₀₀₀ and COPSAC₂₀₁₀ cohorts by domestic dog exposure in early life.

COPSAC2000 Dog exposure					COPSAC2010 Dog exposure			
All % (n)	100% (397)	Yes 14% (55)	No 86% (342)	P-value -	100% (700)	Yes 19% (132)	No 81% (568)	P-value -
Gender-children								
Male% (n)	49% (195)	47% (26)	49% (169)	0.77	51% (360)	55% (72)	51% (288)	0.42
Maternal age at birth (years)								
Mean (SD) ^{†*}	30 (4.5)	29 (4.6)	30 (4.5)	0.09	32 (4.3)	31 (4.7)	33 (4.2)	0.10
Maternal exposures during pregnancy								
Smoking (any) % (n)	24% (94)	38% (21)	21% (73)	0.006*	8% (54)	14% (19)	6% (35)	0.001*
Antibiotic use (any) % (n)	30% (119)	35% (19)	29% (100)	0.43	36% (253)	42% (56)	35% (197)	0.10
Mode of delivery								
Caesarean section % (n)	22% (86)	22% (12)	22% (74)	0.98	22% (151)	20% (26)	22% (125)	0.56
Breastfeeding								
Duration of solely breastfeeding median days [‡]	122 (90-155)	114 (39-152)	122 (92-155)	0.12	122 (45-150)	104 (18-130)	123 (58-151)	0.0004*
Siblings								
Any older children in the home % (n)	39% (147)	31% (16)	40% (131)	0.24	57% (395)	58% (76)	57% (319)	0.80
Filaggrin gene mutations								
Present	13% (49 ^{**})	17% (9)	12% (40)	0.30	11% (72)	11% (58)	11% (14)	0.90
CD14 gene mutations								
CC	30% (89)	32% (13)	30% (76)	0.87	29% (128)	31% (23)	28% (105)	0.72
CT	50% (145)	51% (21)	49% (124)		50% (225)	51% (38)	50% (187)	
TT	20% (59)	17% (7)	21% (52)		21% (93)	18% (13)	22% (80)	
Socioeconomic factors								
Maternal Educational level % (n) [§]				0.02*				<.0001*
Low	60% (223)	78% (39)	57% (184)		8% (55)	11% (15)	7% (40)	
Medium	26%	16%	28%		64%	80%	61%	

	(98)	(8)	(90)		(451)	(105)	(346)	
High	14%	6%	15%		28%	9%	32%	
	(51)	(3)	(48)		(194)	(12)	(182)	
Parental disposition								
Maternal atopic disease	100%	100%	100%	-	54%	52%	54%	0.69
	(397)	(55)	(342)		(374)	(68)	(306)	
Paternal atopic disease	40%	42%	40%	0.78	44%	44%	43%	0.94
	(122)	(14)	(108)		(294)	(57)	(237)	

[§] Low education: elementary, high school, college. Medium education: tradesman certification, bachelor degree. High education: university degree

[§] Wilcoxon rank sum test

[¶] Student's T-test

* SD: standard deviation

** Information on FLG mutation was available in 50 children, but in one of these children information on dog ownership was unavailable.

FIGURE

Figure 1: Kaplan Meier curves demonstrating risk of atopic dermatitis stratified by dog exposure during the first 3 years of life in 2 different birth cohorts. A: COPSAC₂₀₀₀ adjusted HR =0.46 [0.25-0.87], p=0.02. B: COPSAC₂₀₁₀ adjusted HR =0.58 [0.36-0.93], p=0.03

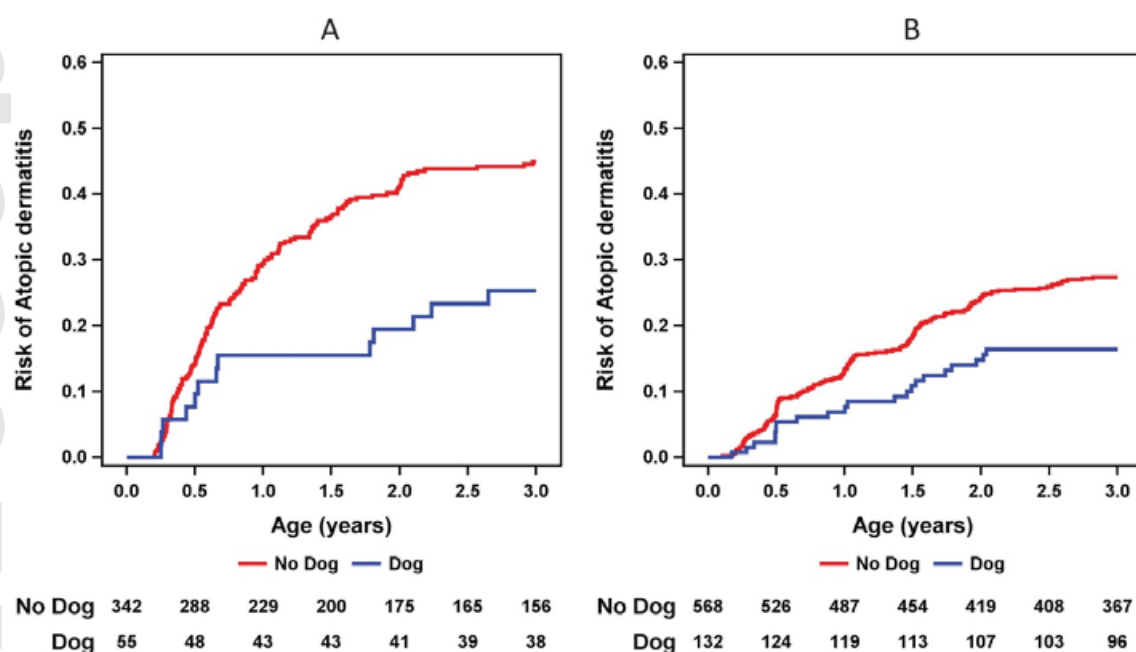


Figure 2: Kaplan Meier curves demonstrating risk of atopic dermatitis stratified by dog exposure during the first 3 years of life in the unselected COPSAC₂₀₁₀ cohort. A: Mothers with atopic disease (physician diagnosed asthma, eczema and rhinitis) $\text{adjusted HR} = 0.39 [0.19-0.82]$, $p=0.01$. B: Mothers without atopic disease $\text{adjusted HR} = 0.92 [0.49-1.73]$, $p=0.79$.

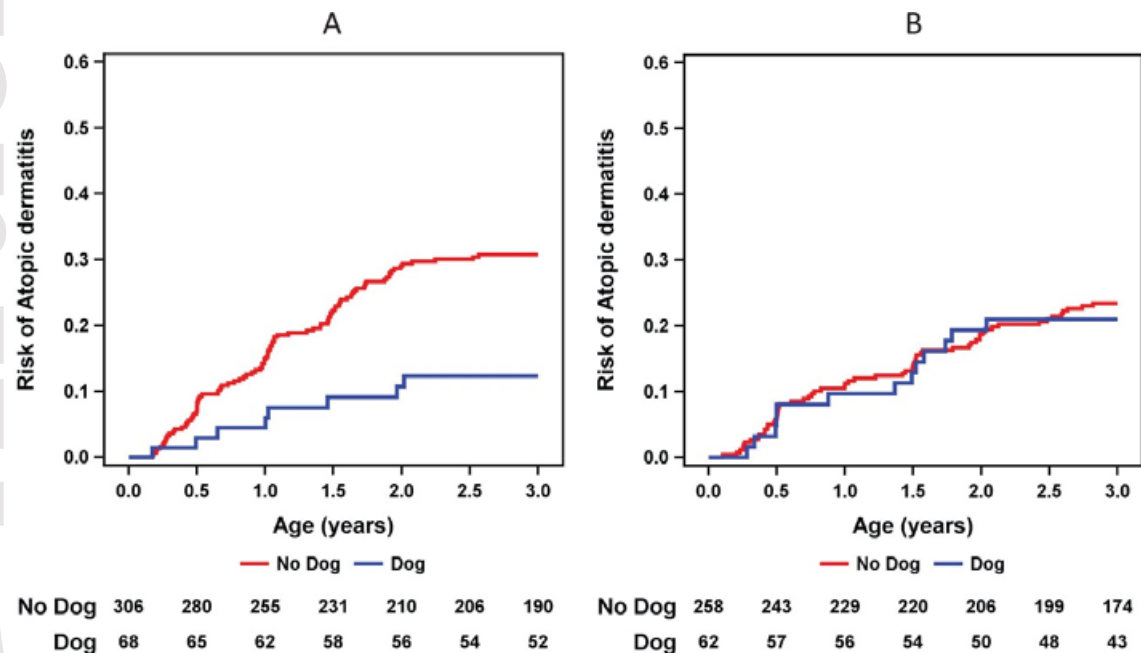


Figure 3: Kaplan Meier curve demonstrating the risk of AD in a dose-related manner with increasing number of dog(s) in the COPSAC₂₀₁₀ cohort $\text{adjusted HR} = 0.58 [0.38-0.89]$, $p=0.01$.

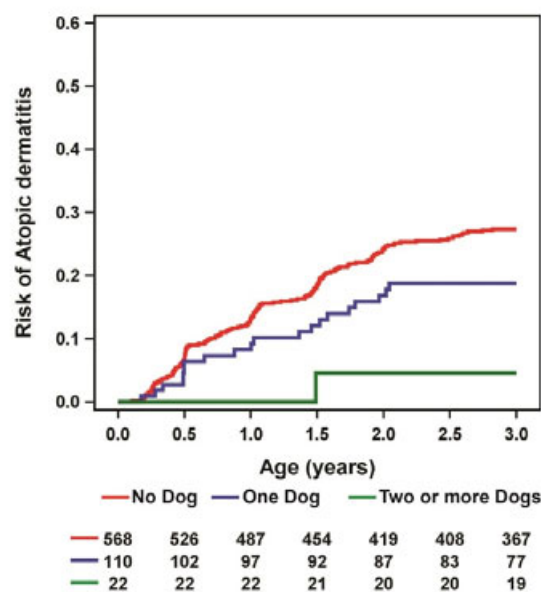
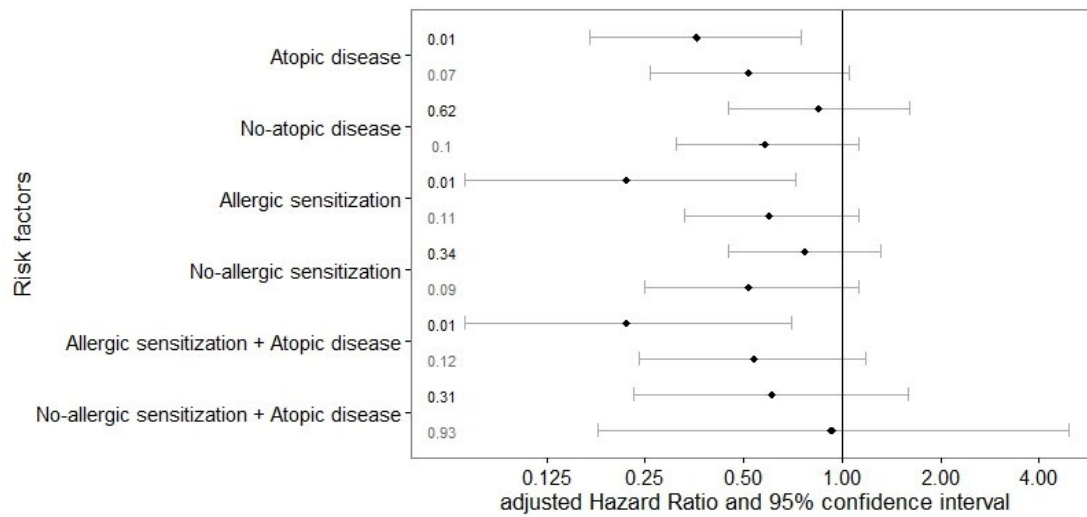


Figure 4: The effect of domestic dog exposure on the risk of atopic dermatitis stratified by maternal (black) and paternal (grey) atopic disease characteristics in the COPSAC 2010 cohort. Overall n=700.



*Atopic disease: parent with doctor diagnosed asthma, eczema, or rhinitis.

No atopic disease: parent without doctor diagnosed asthma, eczema, or rhinitis.

¶ Allergic sensitization: specific-IgE ≥ 0.35 kU/ml

No allergic sensitization: specific-IgE < 0.35 kU/ml.