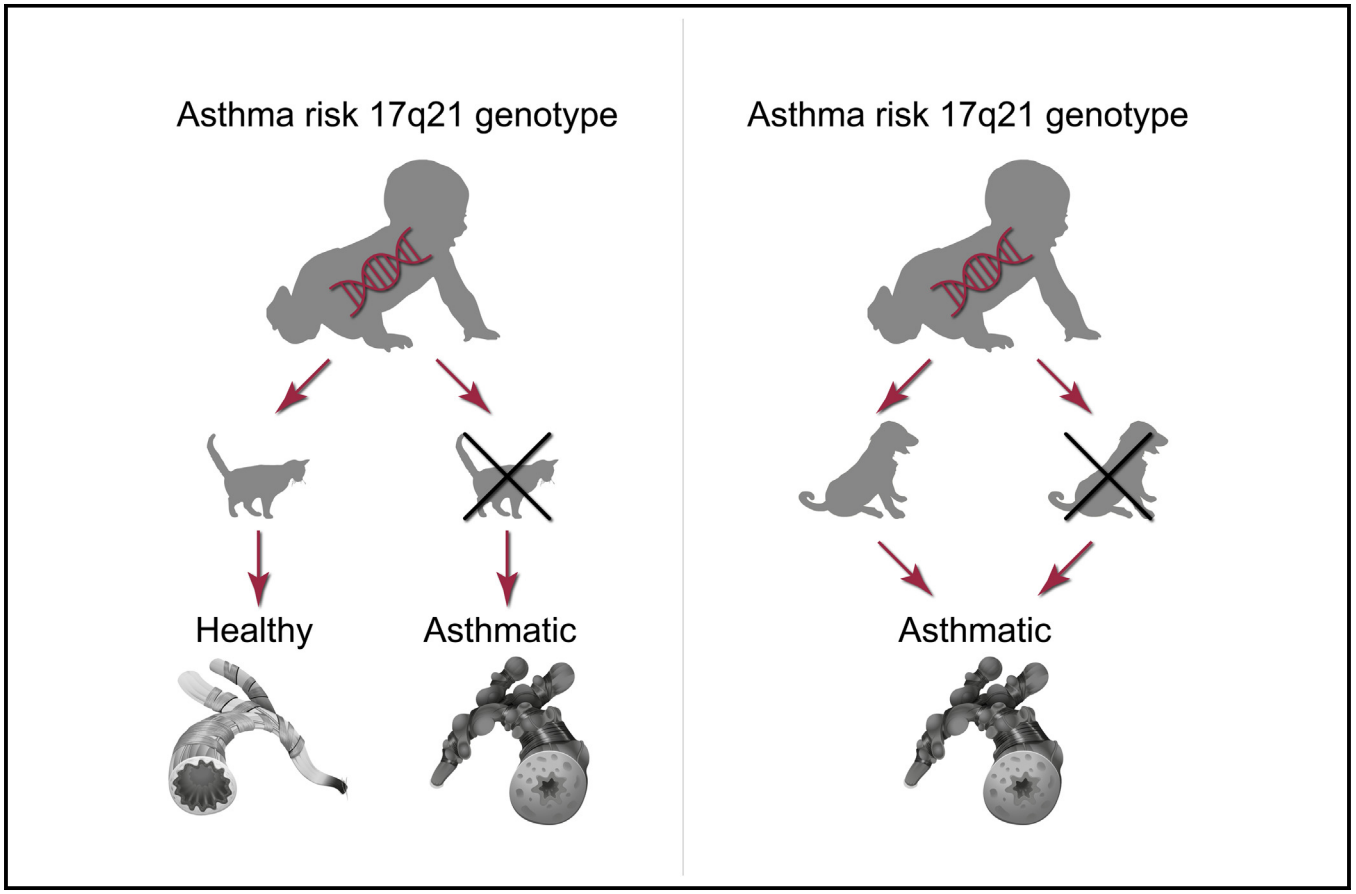
Cat exposure in early life decreases asthma risk from the 17q21 high-risk variant

Jakob Stokholm, MD, PhD,[a,b] Bo L. Chawes, MD, PhD, DMSc,[a] Nadja Vissing, MD, PhD,[a] Klaus Bønnelykke, MD, PhD,[a] and Hans Bisgaard, MD, DMSc[a] *Copenhagen and Naestved, Denmark*

GRAPHICAL ABSTRACT



Background: Early-life exposure to cats and dogs has shown diverging associations with childhood asthma risk, and gene-environment interaction is one possible explanation.
Objectives: We investigated interactions between cat and dog exposure and single nucleotide polymorphism rs7216389 variants in the chromosome 17q21 locus, the strongest known genetic risk factor for childhood asthma.
Methods: Genotyping was performed in 377 children from the at-risk Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$. The primary end point was the development of asthma until age 12 years. The secondary end point was the number of episodes with pneumonia and bronchiolitis from 0 to 3 years of age. Exposures included cat and dog ownership from birth and cat and dog allergen levels in bedding at age 1 year. Replication was performed in the unselected COPSAC$_{2010}$ cohort with follow-up until 5 years of age.
Results: Cat and/or dog exposure from birth was associated with a lower prevalence of asthma among children with the

From [a]COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, and [b]the Department of Pediatrics, Naestved Hospital.

COPSAC is funded by private and public research funds all listed on www.copsac.com. The Lundbeck Foundation (grant no, R16-A1694), Danish Ministry of Health (grant no. 903516), Danish Council for Strategic Research (grant no. 0603-00280B), and Capital Region Research Foundation have provided core support for COPSAC.
Disclosure of potential conflict of interest: H. Bisgaard received consultancy fees from Chiesi Pharmaceuticals and Boehringer Ingelheim, and his institution received grants from the Lundbeck Foundation, Novo Nordisk Foundation, Danish Ministry of Health, and Danish Strategic Research Foundation for other works. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication June 9, 2016; revised June 27, 2017; accepted for publication July 3, 2017.

Corresponding author: Hans Bisgaard, MD, DMSc, COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Ledreborg Alle 34, DK-2820 Gentofte, Denmark. E-mail: bisgaard@copsac.com.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2017.07.044

rs7216389 high-risk TT genotype (adjusted hazard ratio, 0.16; 95% CI, 0.04-0.71; $P = .015$), with no effect in those with the CC/CT genotype (adjusted $P = .283$), demonstrating interaction between cat and dog exposure and the rs7216389 genotype (adjusted $P = .044$). Cat allergen levels were inversely associated with asthma development in children with the TT genotype (adjusted hazard ratio, 0.83; 95% CI, 0.71-0.97; $P = .022$), supporting the cat–rs7216389 genotype interaction (adjusted $P = .008$). Dog allergen exposure did not show such interaction. Furthermore, the TT genotype was associated with higher risk of pneumonia and bronchiolitis, and this increased risk was likewise decreased in children exposed to cat. Replication showed similar effects on asthma risk.

Conclusion: The observed gene-environment interaction suggests a role of early-life exposure, especially to cat, for attenuating the risk of childhood asthma, pneumonia, and bronchiolitis in genetically susceptible subjects. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *MeSH, asthma, cats, dogs, human orosomucoid-like 3 gene protein, gene-environment interaction*

Asthma represents the most common chronic disorder in children and is a major cause of hospitalizations and school absence worldwide.[1,2] Asthma development represents a complex mechanism with a disease trajectory originating from both genetic and environmental effects in early life,[3] but known risk factors only explain a minor proportion of disease variance.

Cat and dog exposure has generally been suspected to increase the risk of childhood asthma, but studies have been inconsistent, showing both increased risk, decreased risk, or no effect of cat and dog exposure on asthma development.[4-8] The type and timing of these exposures might be critical, and the possible effects in early life might be different from those later in life, when the same exposure can lead to different effects. Similarly, we have reported previously a gene-environment interaction between cat exposure from birth and risk of eczema in carriers of the filaggrin nonfunctional mutation, with cat exposure further increasing the risk in carriers.[9]

In the current study we investigated a possible interaction between a genetic variant (single nucleotide polymorphism [SNP] rs7216389) in the chromosome 17q21 locus, the strongest genetic risk factor for early-onset childhood asthma, and cat and dog exposure from birth with respect to development of childhood asthma, pneumonia, and bronchiolitis. Because asthmatic disease related to 17q21 variants develops within the first years of life, any modifying environmental exposures must precede this. We used data from the Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ (COPSAC$_{2000}$) high-risk birth cohort analyzing the longitudinal development of asthma from age 0 to 12 years and replicated the findings in the unselected COPSAC$_{2010}$ cohort from age 0 to 5 years.

Abbreviations used

aHR:	Adjusted hazard ratio
aIRR:	Adjusted incidence rate ratio
COPSAC$_{2000}$:	Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$
HR:	Hazard ratio
IRR:	Incidence rate ratio
LRTI:	Lower respiratory tract infection
ORMDL3:	Orosomucoid-like 3 gene
SNP:	Single nucleotide polymorphism

METHODS

Governance

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 as defined in the European Union's Directive on Good Clinical Practice, the International Conference on Harmonisation's 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.

Study population

The COPSAC$_{2000}$ study included 411 infants born to mothers with a history of asthma enrolled at 1 month of age and followed prospectively for 12 years.[3,10,11] Exclusion criteria were any respiratory symptoms before inclusion, gestational age of less than 36 weeks, and any congenital abnormality or systemic illness. The study was performed according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Copenhagen (KF 01-289/96) and the Danish Data Protection Agency (2015-41-3696). Written informed consent was obtained from both parents.

Clinical surveillance

Medical doctors at the COPSAC clinical research unit were responsible for the diagnosis and treatment of all respiratory and skin-related symptoms. Participants were assessed until age 12 years at the research unit every 6 months for the first 7 years and at additional visits immediately on symptom onset. At every visit, a full physical examination was performed, and personal interviews were guided by structured questions and closed response categories focusing on the child's lung and skin symptoms, medications, health care use, lifestyle, and home environment.

Data validation and quality control followed the guidelines for good clinical practice. Data were stored in a dedicated online database. The data were double-checked against source data and subsequently locked.

Primary end point: asthma

Troublesome lung symptoms were defined to the parents as wheezing or whistling sounds, breathlessness, or persistent troublesome cough severely affecting the child's well-being. The presence or absence of troublesome lung symptoms was recorded as a composite dichotomized (yes or no) score in daily diaries, as previously described.[12] Asthma was solely diagnosed by the COPSAC physicians according to a strict algorithm based on repeated episodes of troublesome lung symptoms, need of intermittent inhaled β_2-agonist, and positive effects of inhaled corticosteroids relapsing after a 3-month test period.[11] Age at asthma diagnosis from 0 to 12 years was used for analysis.

Secondary end point: lower respiratory tract infection

The children were examined, diagnosed, and treated for pneumonia and bronchiolitis by the COPSAC pediatricians in accordance with predefined standard procedures. Clinical pneumonia was defined by troublesome cough accompanied by tachypnea, fever, and abnormal auscultation,[12] whereas bronchiolitis was defined by symptoms of coryza progressing over a few days to cough, tachypnea, chest retractions, and auscultative widespread crepitation and/or rhonchi in a child younger than 2 years of age.[13] Analyses included the number of lower respiratory tract infection (LRTI) episodes from 0 to 3 years of age.