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POPULATION STUDY ARTICLE

Environmental determinants associated with acute otitis media in children: a longitudinal study

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BACKGROUND: Acute otitis media (AOM) is a common pediatric disease and frequent reason for antibiotic treatment. We aimed to identify environmental and host factors associated with AOM and assess which determinants were associated with AOM at specific ages.

METHODS: This study among 7863 children was embedded in the Generation R Study: a population-based prospective cohort study from fetal life onwards. Data on outcome and possible determinants were collected using questionnaires until 6 years. We used generalized estimating equation models to examine associations with AOM with longitudinal odds at different ages, considering correlations between repeated measurements.

RESULTS: Male gender increased odds of AOM in children at 2, 3, and 4 years but not at other ages. Postnatal household smoking, presence of siblings, and pet birds increased odds of AOM. Breastfeeding decreased AOM odds, most notably in the first 2 months of life. No association was found for season of birth, maternal age, ethnicity, aberrant birth weight for gestational age, prenatal smoking, furry pets, and daycare attendance.

CONCLUSIONS: Risk of childhood AOM varies with age. Significant association with AOM was found for gender and breastfeeding at specific ages and for household smoking, presence of siblings, and pet birds at all the studied ages.

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INTRODUCTION

Acute otitis media (AOM) is a common pediatric disease and the most frequent reason for antibiotic treatment in children. It is characterized by the presence of (purulent) fluid in the middle ear accompanied by earache, bulging of the tympanic membrane and fever, and is usually preceded by an upper respiratory tract infection (URTI).[1,2] In the post-pneumococcal vaccination era before the age of 3 years, 60% of children will have gone through at least one episode of AOM, with 24% of children suffering ≥3 episodes.[2,3] The associated frequent consultation of physicians, school absence, and consumption of antibiotics constitute a considerable societal burden.[4,5] The pathogenesis of otitis media is one of the complex associations between genetic, host, and environmental factors.[6,7] Previously, many potential risk factors have been identified, including—but not limited to—daycare attendance, presence of siblings, breastfeeding or lack of breastfeeding, socioeconomic status (SES), prenatal maternal smoking, postnatal exposure to household smoking, and season of birth. AOM is a common disease that afflicts nearly all children in childhood; some children, however, are more prone to it than are others, and some appear more prone to it at a younger age than are others. Likely, not only susceptibility to AOM varies with age but also the effect of certain risk factors on AOM susceptibility. Being breastfed, for example, might lower the risk of AOM in the first year of life—but not beyond.

This study aims to examine associations of potential determinants with AOM at different ages in one model, taking into account correlations between repeated measurements of AOM within the same child.

METHODS

General study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life until young adulthood in Rotterdam, the Netherlands. Details on study design, response rate, and (loss to) follow-up have been published previously.[8] In brief, the Generation R Study aims to identify early environmental and genetic factors affecting children's growth, development, and health. Mothers with a delivery date between April 2002 and January 2006 were eligible for inclusion in the study. The study was approved by the Medical and Ethics Review Board of the Erasmus University Medical Center in Rotterdam, the Netherlands (MEC-2007-413-NL21545.078). Written informed consent was obtained from parents or legal guardians of all 7863 subjects.

Acute otitis media

The following outcomes were collected through parental questionnaires: episodes of otorrhea, earache with fever, and use of eardrops prescribed by family practitioner or ear, nose, and throat surgeon. AOM was defined using these outcomes. Questionnaires were administered at the children's ages of 2, 6, 12, 24, 36, 48 and 66 months (Supplemental Fig. S1).

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Determinants

Prenatal maternal characteristics, child characteristics, and postnatal exposures that might serve as environmental determinants for AOM were selected on the basis of a literature review and data availability in our present study (Supplemental Table S1). Upon enrollment, information was collected on maternal age, parity (nulliparous, multiparous, number of older siblings at birth), and pet keeping (yes; no—dog, cat, bird, rodent). Information on maternal smoking until pregnancy and during pregnancy was obtained by multiple questionnaires. We took maternal educational level (lower, higher) to represent SES, as maternal education level has been previously described as a consistent socioeconomic predictor in cardiovascular disease, pregnancy outcomes, and early childhood behavior.[9,10] Data on postnatal household smoking were collected at 2, 24, 36, and 66 months after birth of the child. Hospital registries provided information on the child's gender, ethnicity (Western, non-Western), season of birth, gestational age at birth, and birth weight. We calculated birth weight for gestational age. In the Netherlands, breastfeeding is encouraged at least until the age of 6 months (http://www.rivm.nl/en). Questionnaires administered at 2, 6, and 12 months provided information on breastfeeding (yes, no) and/or daycare attendance (yes, no). The Dutch national vaccination schedule (including—but not limited to—antigens against *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, and *Neisseria meningitidis*) was established in 1957 and currently covers >95% of all Dutch children (http://www.rivm.nl/en). Influenza vaccination is not included and is only administered to children with specific underlying disease, such as cystic fibrosis, cardiac disease, or severe early-onset asthma. Consequently, no data on vaccination status were collected.

Statistical analysis

Statistical analyses and imputation were performed using R (www.r-project.org, R version 3.3.3, released March 2017). Screening of missing values among covariates concluded that the data set had an arbitrary missing data pattern. Missing data were imputed to reduce potential bias using the Markov chain Monte Carlo method. We used generalized estimating equation (GEE) models to examine associations with AOM of different covariates with longitudinal odds at the ages of 2, 6, 12, 24, 36, 48, and 66 months. Correlations between repeated measurements of outcome within the same child were taken into account. As part of the GEE model analysis, we used multiple linear regression analysis through the "geeglm" function in R to provide a way of accounting for potentially confounding variables that may have been included in the model. We checked for the potential interaction of time with each covariate and included in our model only the interaction terms time–gender and time–breastfeeding as it increased goodness of fit. Other interaction terms between covariates were tested, that is, household smoking–SES; prenatal smoking–postnatal household smoking; breastfeeding–SES; breastfeeding–age of the mother; age of the mother–SES; siblings–daycare, but none improved the model. Nonlinearity of the association between time and gender and between time and breastfeeding were investigated by logistic regression models with natural cubic splines of three knots. As no major differences in values between imputed and non-imputed data were found (Table 1 and Supplemental Table S2), only the results from imputed analyses are presented. Odds ratios (ORs) are presented with their 95% confidence intervals; level of significance was set at $p = 0.05$.

RESULTS

Study population and baseline characteristics

Child and maternal baseline characteristics relating to 7863 children are presented in Table 1. The children's gender distribution was equal, and the cohort included more children of Western ethnicity (66.6%) than children of non-Western descent. Most of the children were breastfed, and a small majority of children attended daycare. Cats were the most common household pet, followed in prevalence by dogs, rodents, and birds in that order. A small majority of mothers were of higher SES and a small majority were nulliparous. Although 75.5% of mothers had not smoked at all during pregnancy, >40% reported postnatal household smoking.

Table 1. Characteristics of children and their mothers based on imputed data

Characteristic	Total study population
Children	
No. (%)	7863 (100)
AOM, yes (*n* [%])	
Age 2 months	148 (1.9)
Age 6 months	1005 (12.8)
Age 1 year	2508 (31.9)
Age 2 years	2978 (37.9)
Age 3 years	2282 (29.0)
Age 4 years	2379 (30.3)
Age 5–6 years	2896 (36.8)
Sex, *n* (%)	
Male	3965 (50.4)
Female	3898 (49.6)
Birth weight corrected for gestational age, SDS	−0.08
Ethnicity	
Western	5240 (66.6)
Non-Western	2623 (33.4)
Season of birth, *n* (%)	
Spring	1838 (23.4)
Summer	2138 (27.2)
Fall	2145 (27.3)
Winter	1742 (22.2)
Breastfed ever, yes (*n* [%])	7188 (91.4)
Daycare at 6 months, yes (*n* [%])	4241 (53.9)
Pet in household, yes (*n* [%])	
Rodent	373 (4.7)
Dog	586 (7.5)
Bird	163 (2.1)
Cat	1845 (23.5)
Mothers	
Age at intake, median (IQR)	31.0 (27.3–34.0)
Educational level, *n* (%)	
Higher	4264 (54.2)
Lower	3599 (45.8)
Parity, *n* (%)	
Nulliparous	4418 (56.2)
Multiparous	3445 (43.8)
Smoking during pregnancy, *n* (%)	
No	5937 (75.5)
Stopped when pregnancy was known	697 (8.9)
Yes	1229 (15.6)
Postnatal household smoking, yes (*n* [%])	3192 (40.6)

IQR interquartile range

Overall, the prevalence of AOM in the population increased from 1.9% at 2 months of age to 37.9% at the age of 2 years. Between 3 and 4 years of age, prevalence of AOM declined to approximately 30%, before increasing once more at the school-going age of 5–6 years. Thus the probability of acquiring AOM varies over time in the first 6 years of life (Fig. 1).

AOM and its determinants

The purported risk factors for AOM that were tested are presented in Table 2. Gender was not associated with altered odds of AOM when we looked at the whole population until 6 years of age. When we stratified this association with time, however, girls had slightly lower odds of acquiring AOM at 2, 3, and 4 years of age (Fig. 2). Similarly, we stratified the association of breastfeeding (OR 0.80; $p < 0.040$) and AOM with time. Lower odds of acquiring AOM in those who were breastfed were found from 0 to 2 months of age but not beyond (Fig. 3). Prenatal smoking—regardless of whether the mother quit smoking upon confirmation of pregnancy or continued until childbirth—was not associated with AOM susceptibility in childhood. Postnatal household smoking, however, was associated with a higher risk of AOM among children (OR 1.12; $p = 0.013$). Other associations that increased a child's AOM susceptibility were with the presence of older siblings (OR 1.07 per sibling; $p < 0.001$) and in the presence of birds as household pets (OR 1.25; $p < 0.013$). No associations with AOM were found among subjects with furry pets (dogs, cats, or rodents). Season of birth, birth weight for gestational age, maternal age, ethnicity, and SES were not associated with altered AOM susceptibility.

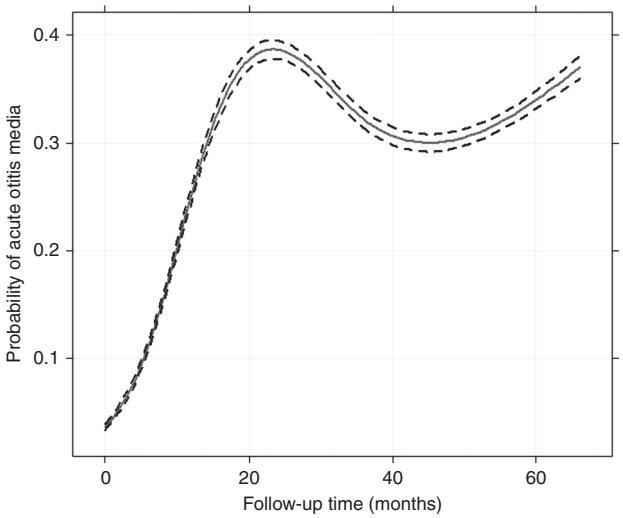

Fig. 1 The shape of the plot illustrates the probability of developing acute otitis media in time from 2 until 66 months of age in the general population without taking into account genetic, host, or environmental risk factors

Table 2. Determinants associated with acute otitis media in children

Determinants	OR (95% CI)[a]	*p* value
Female gender	0.93 (0.82, 1.06)	
Breastfed	**0.80** (**0.64**, **0.99**)	$p = 0.040$
Season of birth		
Spring	Ref.	Ref.
Summer	0.94 (0.87, 1.01)	
Fall	0.98 (0.92, 1.06)	
Winter	1.02 (0.95, 1.10)	
Higher maternal age	1.00 (0.99, 1.00)	
Non-Western ethnicity	1.04 (0.98, 1.10)	
Low socioeconomic class	1.02 (0.94, 1.10)	
Older siblings[b]	**1.07** (**1.03**, **1.11**)	$p < 0.001$
Below or higher than 2 SD birth weight for gestational age	1.01 (0.98, 1.03)	
Maternal smoking until pregnancy known	1.09 (0.95, 1.25)	
Maternal smoking during pregnancy	1.09 (0.92, 1.29)	
Postnatal household smoking	**1.12** (**1.02**, **1.22**)	$p = 0.013$
Pet keeping		
Dog	1.05 (0.95, 1.16)	
Cat	0.98 (0.92, 1.04)	
Bird	**1.25** (**1.05**, **1.50**)	$p = 0.013$
Rodent	0.91 (0.80, 1.03)	
Daycare attendance	0.97 (0.91, 1.03)	

CI confidence interval, *OR* odds ratio
[a]OR (95% CI) in bold when $p < 0.05$
[b]Maternal (multi)parity upon enrollment was used as a proxy for the child having siblings; OR is cumulative per sibling

DISCUSSION

While nearly all children go through AOM during childhood, some children may be more susceptible to frequent episodes of AOM than are others. The odds of acquiring AOM are influenced by many factors. This study found gender, breastfeeding or lack thereof, household smoking, number of siblings, and having pet birds to be influencing factors in the studied population. Gender and breastfeeding were associated with AOM only at specific ages.

Being a boy increased an individual's odds of acquiring AOM, specifically between 2 and 4 years of age. Results of previous studies on gender and AOM were conflicting. Studies on AOM in populations aged between 0 and 3 years also reported a higher risk of AOM among boys, although some of these studies showed this association only in boys aged <1 year.[2,11–14] All but one previous study that found no association with gender concerned older children (3–16 years).[15–17] This study with its design based on repeatedly measured outcomes at different ages was able to zoom in at which specific age range gender was associated with AOM in childhood.

Associations between breastfeeding and AOM have been thoroughly investigated. The reported positive effects of breast-feeding included lower probability of AOM, of recurrent AOM, and of otitis media with effusion; even short-term—non-exclusive—breastfeeding was found beneficial over formula feeding.[18,19] In the present study, breastfed children had lower odds of AOM before 2 months of age but not beyond. Previous studies, however, reported lower rates of AOM up to 2 years of age for children exclusively breastfed for at least 6 months.[2,12,20,21] In the Netherlands, breastfeeding is encouraged for at least 6 months. Still, maternity leave from work is only 16 weeks, of which 12 weeks are usually taken after childbirth. Our data set did not include information on whether children were exclusively breastfed. A large proportion of mothers may have introduced formula feeding after 2–3 months, which could explain why the protective effect of breastfeeding in our population entailed a shorter duration.

Breastfeeding is associated with a lower rate of URTIs through the influence of secretory IgA, cytokines, and long-chain fatty acids in breast milk, which are paramount to development of the infant's immune system.[22] This might explain why in our study breastfeeding was associated with a lower risk of AOM in children. Season of birth may be associated with either an increase or

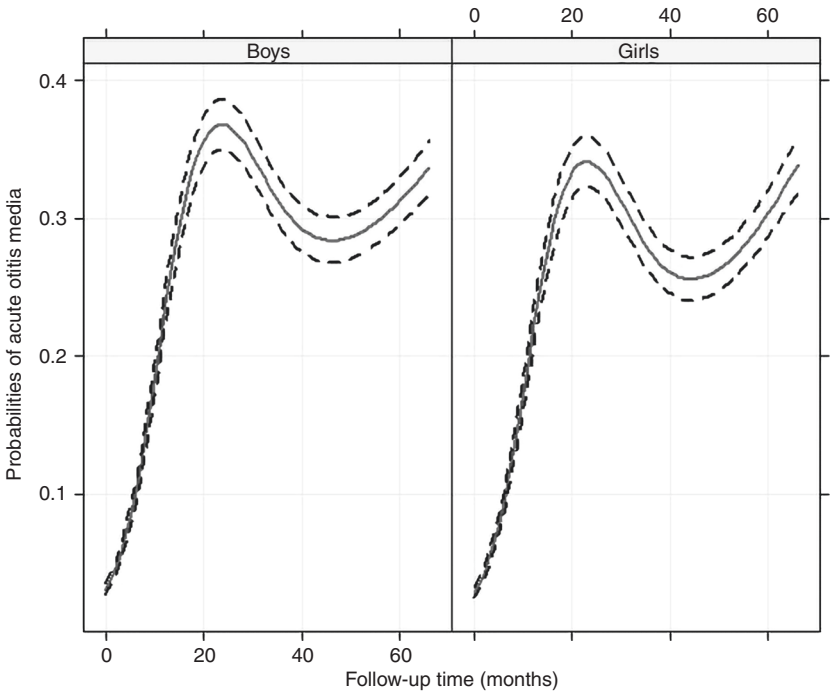

Fig. 2 Difference in the probability of developing acute otitis media (AOM) over time for boys (left) and girls (right) when other child, maternal, and environmental risk factors are similar. In this plot, the subjects were born in the fall, were breastfed, attended daycare, had no siblings or pets in the household, maternal age was 31.3 years, mothers did not smoke prenatally, and the child was not exposed to household smoking after birth. The probability of developing AOM was significantly different between boys and girls at ages 24, 36, and 48 months ($p < 0.001$)

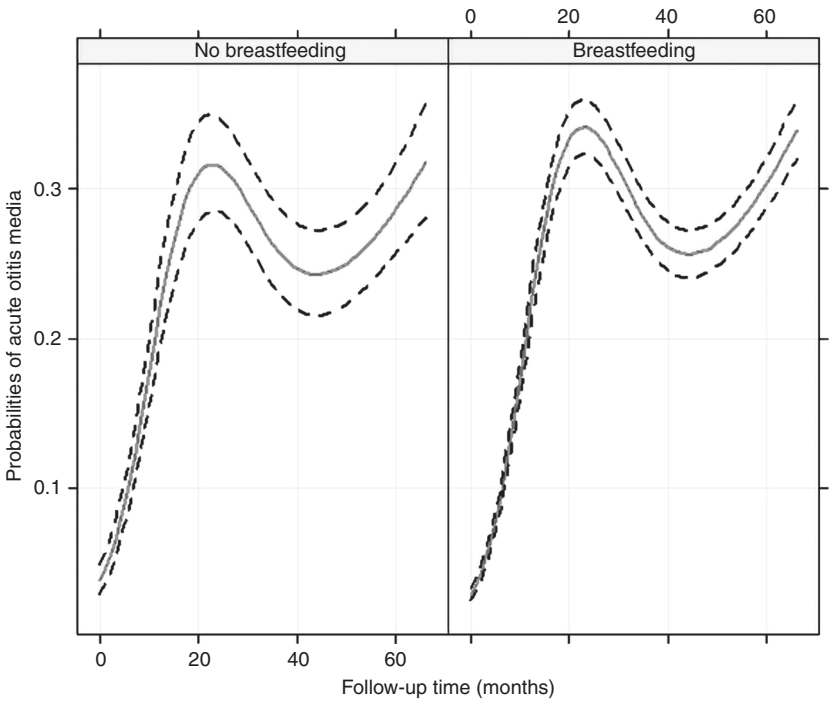

Fig. 3 Difference in the probability of developing acute otitis media (AOM) over time for subjects who were not breastfed (left) and who were breastfed (right) when other child, maternal, and environmental factors are similar. In this plot, the subjects were born in fall, attended daycare, had no siblings or pets in the household, maternal age was 31.0 years, mothers did not smoke prenatally, and the child was not exposed to household smoking after birth. The probability of developing AOM among subjects who were breastfed had significantly declined from birth to 2 months of age ($p = 0.028$ and $p = 0.038$, respectively)

decrease in the rate of URTIs, depending on the season. The amount of viral pathogens in the environment in the fall and winter is higher than that in the spring and summer. In the present study, we found no evidence of altered odds of AOM in relation to season of birth. The literature on this issue is contradictory; some studies report that birth in the fall would carry higher odds of AOM, whereas other studies report lower AOM rates among subjects born in the fall.[23–25]

The present study did not find an association between AOM and (number of) siblings and between AOM and daycare attendance. While many previous studies reported higher odds of AOM for children who had siblings, two studies concurred with the present one finding no statistical difference in the likelihood of AOM between subjects with or without siblings.[12,14,15,18,26,27] One study focused on children who attended daycare—which in itself is a reason for significantly increased viral pathogen exposure that may have diminished the effect of having siblings in that particular study.[15] Daycare attendance indeed has often been related to increased risk of AOM, with risk further increasing for children who attend daycare for a longer period (>12 months).[2,21,28] Daycare attendance rates vary widely among European countries, which could perhaps account for the differences between our findings and those of other studies. Daycare attendance rates of 3-year-olds ranged from 3–10% of children in Iceland, Slovenia, Portugal, Poland, Italy, and Denmark to 60–70% in Austria and the Netherlands (http://appsso.eurostat.ec.europa.eu). Where in a recent Danish study it was shown that starting attending daycare before the age of 12 months carried a higher risk of experiencing >3 episodes of AOM at 18 months, and to a lesser extent at 7 years of age, no such association was found in our studied population. Moreover, owing to the relatively short maternity leave of 10–12 weeks after childbirth in the Netherlands, it is likely that most children in our population started attending daycare at the age of 3 months. Daycare attendance in this study was measured at 6 months. Whether early daycare attendance affected results is unclear.

Our study found no association between childhood AOM and keeping a family cat, dog, or rodent but did find higher odds of AOM in children with a pet bird at home. Keeping furry pets such as cats, dogs, rodents, and rabbits, has been associated not only with increased rates of rhinitis and wheezing but also with decreased odds of suffering recurrent URTIs, which was the case in the population we studied.[27–29] This disparity has been attributed to selection bias through parental allergy, which increases not only the odds of recurrence of URTIs but may also lead to parents choosing not to have a pet.[28,30]

Public health in general is influenced by health behaviors associated with socioeconomic disparities. Literature on the association between SES and AOM has been contradictory; some studies reported absence of an association and others reported a negative effect of lower SES on AOM.[12,14] The most important unhealthy behavior is smoking. We studied both prenatal maternal smoking and household smoking. We found that household smoking raised the odds of AOM, which was also reported in recent literature including two meta-analyses[11,21,31–33] A few other studies found no convincing association.[2,12,16,34] We found no association between prenatal smoking and AOM, which is in agreement with a recent meta-analysis.[31,32]

In the present study, we corrected birth weight for gestational age for which we found no association with AOM. In previous studies, birth weight was often studied separately from gestational age. In twins where one child is OM-prone and the other is not, it has been shown that the twin with a history of OM weighed significantly less at birth.[12,26] Still, a low birth weight can be the result of preterm birth, which in itself can be related with factors that might have an effect on AOM in the child later in life; that is, SES, infections during pregnancy, and maternal (household) smoking, which is why in the present study birth weight was corrected gestational age.

Our study found no association between AOM and ethnicity. Literature on ethnicity is more difficult to compare as it encompasses society and culture in different areas on the globe. While several studies did not find a difference in AOM odds between different ethnicities, in other studies subjects of Western descent had higher odds of AOM than did subjects from Asian or African descent.[2,25,35] The discrepancy between our results and the latter may be due to the ethnic composition of the non-Caucasian subjects in our study—Cape Verdean, Dutch Antillean, Moroccan, Surinamese-Creole, Surinamese-Hindustani, and Turkish descent versus (sub-Saharan) African and Asian descent.[8]

In general, after thoroughly correcting for all covariates and taking into account repeated measurements, effect sizes found in this study were small. Perhaps the impact of individual determinants is overestimated in literature, especially when they were measured only once, or when a smaller number of environmental factors were measured for adequate correction. Still, as AOM is so common in children, even improving determinants with small effects could have an impact on public health on a larger scale.

Our study has strengths and limitations inherent to the study design. Strengths of this study are its sample size and its appreciation of repeated measurements in a GEE model. Thus we were able to study AOM and its determinants with respect to ageing, which in itself has an effect on AOM susceptibility. This study was limited by the availability of covariates. In addition, we used parent-reported outcomes that may carry the risk of recall bias and possibly overdiagnosis. Previous studies, however, have shown the diagnostic value of particularly earache, fever, and otorrhea in AOM with a sensitivity and specificity of 71% and 80%, respectively.[36–38] In other studies, specific symptoms such as ear tugging/rubbing and restless sleep were not significantly associated with occurrence of AOM.[39] Still, as AOM is a painful condition often accompanied with fever and/or otorrhea, it is generally well recalled by parents. Recall accuracy was further improved by the regular administration of questionnaires. Not performing otoscopic examination at each occurrence of otorrhea did hold the moderate risk of including some otitis externa cases. Approximately 7% of all children experience an episode of otitis externa before the age of 4 years, which makes it a less common cause of otorrhea than is AOM.

Lastly, we did not address genetic factors that might influence susceptibility to AOM in children. Genetic susceptibility to AOM is not well understood. Heritability has been established in twin and family studies, in which a fraction of phenotype variability attributed to genetic variation estimated between 0.22 and 0.73.[40] Recently, the FNDC1 gene was found associated with increased risk of AOM in childhood.[7] Still, this disease susceptibility variant in itself constitutes only a modestly increased risk of AOM in this likely polygenic and complex trait. Moreover, environmental factors and genetic as well as epigenetic mechanisms are interlinked. For instance, (maternal) smoking can lead to increased DNA methylation, which in turn causes decreased expression of genes likely affecting disease susceptibility. This only further emphasizes the complexity of the etiology of complex traits such as AOM in childhood.

CONCLUSION

AOM susceptibility in childhood varies with age. Male gender, breastfeeding, household smoking, and the presence of siblings and pet birds were found significantly associated with susceptibility to AOM. Gender and breastfeeding were associated with AOM only at specific ages. Although individual determinants showed small effect sizes, improving these could benefit public health on a larger scale.

DATA AVAILABILITY

The data are available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

G.v.I. conceptualized and designed the study, performed the statistical analyses, and drafted the manuscript; C.M.P.I.C. assisted in conceptualizing and designing the study, assisted in data collection, supervised the statistical analyses, and reviewed the manuscript; C.E.T. coordinated and performed statistical analyses and assisted in drafting the manuscript; L.D. provided comments and consultation regarding statistical analyses and the manuscript; H.A.M. contributed to the original data collection of the Generation R Study and reviewed the manuscript for intellectual content; V.W.V.J. initiated and designed the Generation R Study, supervised data collection for the Generation R Study, and reviewed the manuscript; H.R. made important contributions the design of the Generation R study and reviewed the manuscript for important intellectual content; R.J.B.d.J. critically revised the manuscript and was responsible for the infrastructure of the study; M.P.v.d.S. conceptualized and designed the study, supervised analyses, and drafting of the manuscript; and all authors approved the final manuscript as submitted.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-019-0540-3) contains supplementary material, which is available to authorized users.

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