


ORIGINAL ARTICLE

Identifying distinct trajectories of acute otitis media in children: A prospective cohort study

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Abstract

Objectives: To identify possibly distinct acute otitis media (AOM) trajectories in childhood and identify determinants associated with specific AOM trajectories. To explore which child will become prone to recurrent AOM episodes and which will not.
Design: Population-based prospective cohort study among 7863 children from birth until 10 years and their mothers.

Methods: This study was embedded in the Generation R Study: a population-based prospective cohort study. Data on AOM and determinants were collected by repeated parental questionnaires. Distinct AOM trajectories within the population were identified with latent-class analyses. Next, using multivariate analysis we checked whether specific determinants were associated with specific trajectories.

Results: Three distinct trajectories were identified; that is, *non-otitis prone*, *early AOM*—that is children who suffered AOM episodes until 3 years of age but not beyond, and *persistent AOM*—that is children who remained otitis-prone. Male gender (OR: 1.26, CI: 1.11-1.43) and day-care attendance (OR: 1.31, CI: 1.06-1.60) were associated with increased odds of early AOM. Breastfeeding was beneficial for children in both the early-AOM and persistent-AOM trajectories (OR: 0.78 and 0.77, respectively). Birth in the summer or autumn as compared with birth in the spring decreased odds of AOM only in the persistent-AOM trajectory. Half of all AOM-prone children recovered after the age of 3 years.

Conclusion: Specific determinants are associated with different AOM trajectories. Future research is needed to better predict which child will remain otitis-prone and which recovers after the age of 3 years to better tailor treatment towards the needs of the individual child.

Abbreviations: AOM, acute otitis media; ENT, ear, nose and throat; LCA, latent-class analysis; PCV, pneumococcal conjugate vaccine; SES, socio-economic status; URTI, upper respiratory tract infection.

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1 | INTRODUCTION

Acute otitis media (AOM) is a common disease of childhood, and frequent reason for doctor visits and antibiotic treatment. This infectious disease is defined by fluid in the middle ear, and is commonly characterised by earache, fever and possibly otorrhoea. It is often preceded by an upper respiratory tract infection (URTI).^{1,2} Approximately 60% of children will have gone through at least one episode before the age of 3 years, one quarter of whom will have suffered three or more episodes.^{2,3} Management of AOM puts a heavy burden on healthcare expenditures, with annual costs in the United States estimated at US\$ 4.3 billion per year.⁴ The pathogenesis of AOM is one of complex associations between environmental, host and genetic factors.^{1,5-7} Certain factors in a child's environment are related to an increase or decrease in viral pathogens, which in turn is associated with altered incidence of URIs—and thus of ear infections. These factors include having older siblings, day-care attendance, season of birth, pet keeping, breastfeeding and socio-economic status (SES) in general.⁸⁻¹⁰ Maternal factors with a proposed impact on childhood AOM include prenatal and postnatal (household) smoking and maternal age.¹¹ Host factors include the child's gender and ethnicity.¹² Heritability of AOM is well-established in family studies, sibling and twin studies, but genetic susceptibility of AOM is as yet not well understood.^{13,14}

Due to the complex pathogenesis of AOM, with numerous host, environmental and genetic determinants involved, identifying at the earliest possible age whether a child will become otitis-prone is not easy. Group-based trajectory modelling is a valuable statistical approach to identify different trajectories in childhood based on AOM susceptibility.

In a prospective cohort study among 7863 children from birth until 10 years, we aimed to identify different AOM trajectories. Secondly, we examined whether specific factors were indeed associated with a specific AOM trajectory.

2 | METHODS

2.1 | General study design

This study was conducted in the framework of the Generation R Study, a population-based prospective cohort study from foetal life onwards in Rotterdam, the Netherlands.¹⁵ The Generation R Study addresses early environmental and genetic factors affecting growth, development and health of children and their mothers. Pregnant women with an expected delivery date between April 2002 and January 2006 were eligible to participate. Children born from these pregnancies form a birth cohort that is followed until young adulthood.¹⁵ The study has been approved by the Medical 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 7,863 subjects.

Key Points

- Acute otitis media (AOM) is a common paediatric disease with a complex pathogenesis with numerous host, environmental and genetic factors involved.
- We identified three distinct developmental trajectories in childhood based on susceptibility to AOM; that is, a child not being prone to AOM, a child indeed being prone to AOM and a child being prone to AOM only until 3 years of age.
- In the latter subgroup, male gender and day-care attendance significantly increased the odds of acquiring AOM, whereas breastfeeding decreased these odds in both early- and persistent-AOM-prone subjects.
- Percentage of children who were breastfed at 6 months was highest among children not prone to AOM.
- Season of birth was associated with AOM only in children who remained otitis-prone through childhood.

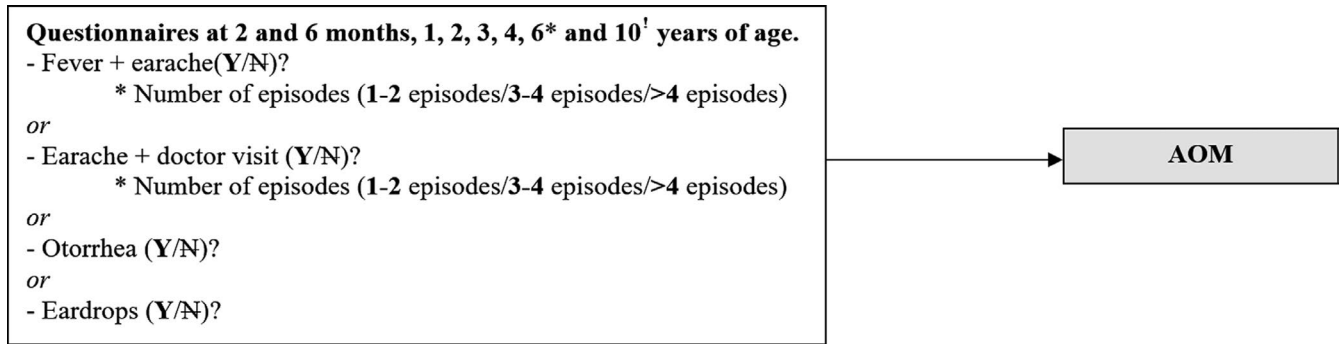
2.2 | Acute otitis media

Parents completed questionnaires on episodes of earache with fever, otorrhoea and use of eardrops per subscription by family practitioners or ENT surgeon. Data were collected at 2 and 6 months, annually between 1 and 4 years, and then by the age of 6 and 10 years (Figure 1). Numbers of questionnaires returned per age are shown in Figure 2. Children for whom fewer than three questionnaires were returned were excluded from further analyses ($n = 2009$).

2.3 | Determinants

Questionnaires were used to collect data on prenatal maternal characteristics, child characteristics and environmental determinants (Table S1). Information on maternal age at birth, parity (nulliparous; multiparous; number of older siblings at birth) and pet keeping (yes; no—dog, cat, bird, rodent) had been collected upon enrolment in the Generation R Study during pregnancy. Maternal education level has been previously described as a consistent socio-economic predictor.¹⁶ Data on maternal education level (lower; higher) were used as a proxy for SES and were collected at the child's age of 6 years. Information on maternal smoking until pregnancy and during pregnancy was obtained from multiple questionnaires.

Information on gender, birthweight and gestational age at birth was retrieved from hospital registries. Birthweight for gestational age was calculated. Data on ethnicity (Western; non-Western) and postnatal smoking were collected through parental questionnaires. Postnatal smoking was assessed at the child's ages of 2 months, and 2, 3 and 6 years. In the Netherlands, breastfeeding



* Questionnaire at 6 years was sent between 60 and 72 months of age with mean age of 66 months.

† Questionnaire at 10 years was sent between 108 and 132 months of age with mean age of 120 months

FIGURE 1 Flow chart of questionnaire data used to define AOM phenotype and control status

is encouraged at least until the age of 6 months (<http://www.rivm.nl/en>). Questionnaires at 6 and 12 months provided information on breastfeeding (yes; no) and/or day-care attendance (yes; no).

2.4 | Statistical analysis

The first aim of the analysis was to identify and describe distinct subgroups within the population that follow a specific AOM trajectory. Different trajectories were identified by latent-class analyses (LCA) using Mplus version 8 (<https://www.statmodel.com/index.shtml>) on the basis of repeated measurements of AOM outcome. LCA was used to classify subjects into homogeneous trajectories after imputation. The number of latent classes was determined on the minimum Bayesian information criterion first and minimum size of at least 5% of the population next. The latter criterion was introduced to eliminate small groups of outliers of limited clinical relevance. We created 2, 3, 4, 5 and 6 latent classes, compared goodness of fit and BIC, and produced plots of trajectories of each model (Figure S1A-E and Table S2). Clinical relevance of different (number of) trajectories was taken into account when a further subdivision of latent classes would only slightly increase goodness of fit.

The second aim of the analysis was to assess whether determinants were associated with membership of specific AOM trajectories. First, screening of missing values among determinants concluded an arbitrary missing data pattern. To reduce potential bias, missing data were imputed using the Markov chain Monte Carlo method (Table S3). IBM SPSS Statistics software (version 24.0.0.1 for Windows) was used for imputation. No major differences were observed between imputed and non-imputed data (Table 1 and Table S4); thus, only results based on imputed data are presented. Next, univariate analyses of determinants associated with membership of a specific trajectory were performed. The non-otitis-prone trajectory served as reference category. Upon examination of the correlation matrix, no multicollinearity between determinants was detected. Determinants associated with a trajectory in univariate analysis with $P < 0.05$ were selected for inclusion in the multivariate model (Table S5). Multivariate analysis was performed; odds ratios (ORs) and their 95% confidence intervals are

presented (Table 2). Determinants that showed subthreshold association in univariate analyses with $P > 0.05$ and $P < 0.15$ were added to the multivariate model, but this did not alter outcome (Table S6). Data of subjects for whom fewer than three questionnaires had been returned—and were excluded from analyses—were compared with data of the entire study population to assess whether values were missing at random (Table S7).

3 | RESULTS

Characteristics of the study population are presented in Table 1. The population totalled 5854 children and their mothers. There was a light preponderance of girls (50.1%), and 72.5% of all children were of Western descent. One third of the population had been breastfed until at least 6 months of age, and two thirds went to day care at 6 months of age. Birth rates in the winter were lower than birth rates in the other three seasons, and cats were the most common family pet (24.7%). Sixty-eight percent of mothers had higher SES, and 57.6% was pregnant of their first child upon inclusion; 22.3% smoked when pregnancy was discovered, and almost 60% of these women continued smoking throughout pregnancy. One third of all subjects grew up exposed to household smoking.

Three distinct AOM trajectories could be distinguished (Figure 3). One trajectory comprised *non-otitis-prone* children; the second consisted of children prone to AOM only in the first 3 years of life (*early AOM*); and the third concerned children who remained otitis-prone throughout (*persistent AOM*). When in LCA, the number of trajectories was increased from three to four, goodness of fit did marginally improve, but this only subdivided the early-AOM trajectory into two smaller fractions without creating a new distinct trajectory, and thus not of clinical relevance (Figure S1B-C). Further increase in the number of trajectories provided only small groups of outliers comprising $< 5\%$ of the population (Table S2).

The non-otitis-prone trajectory totalled 3067 subjects (52.4%). Children in this trajectory had a lower birth rate in the spring and more were breastfed compared with children in the other trajectories. In the early-AOM trajectory ($n = 1335$, 22.8% of total population),

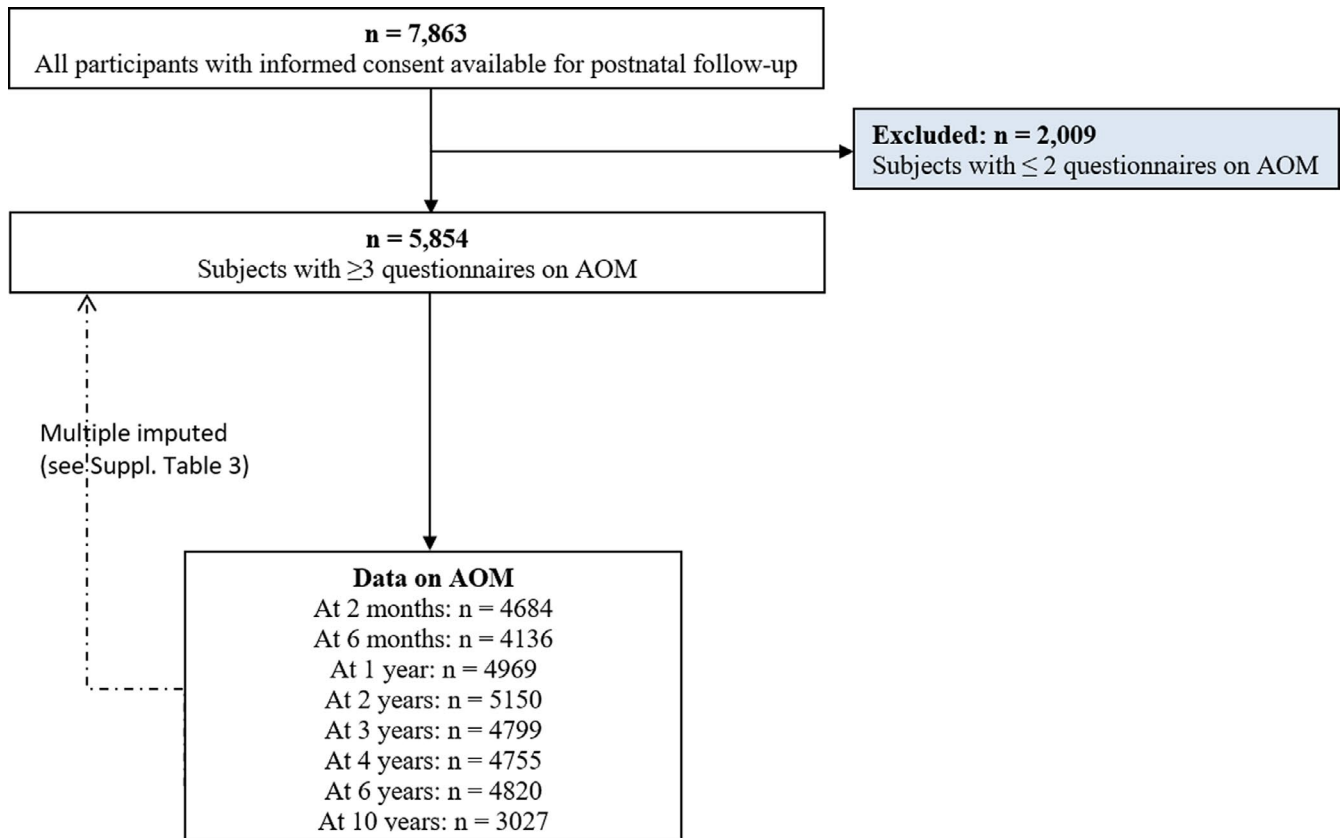


FIGURE 2 Flow chart of the study population

there was a preponderance of boys (53.9%) and slightly more subjects were of Western descent than of non-Western descent. More children attended day care (73.2%) compared with children in the other trajectories (66.7% and 65.3%), and a higher proportion of subjects grew up in a household of higher SES. Persistent AOM held for 24.8% ($n = 1452$) of the population. Compared with the other trajectories, a higher proportion of these children was exposed to household smoking and grew up in a household of lower SES with more often a cat, dog or both.

Multivariate analysis showed which specific determinants altered odds of acquiring AOM per trajectory, compared with subjects who were non-otitis-prone (Table 2). Both male gender (OR: 1.26, $P = 0.001$) and day-care attendance (OR: 1.31, $P = 0.015$) were associated with increased odds of early AOM. Having been breastfed until at least 6 months of age showed decreased odds of acquiring AOM in all otitis-prone children, with OR 0.78 ($P = 0.003$) and OR 0.77 ($P = 0.002$) in early AOM and persistent AOM, respectively. Birth in the summer (OR: 0.74, $P = 0.002$) and autumn (OR 0.82, $P = 0.04$) was associated with decreased odds of acquiring AOM in persistent AOM, but this effect was not found in early AOM. Exposure to household smoking and having siblings had a negative effect in univariate analyses in the persistent-AOM trajectory. This effect disappeared, however, in multivariate analyses. Similarly, potential effects of SES, maternal age and aberrant birthweight for gestational age were not found in multivariate analysis (Tables S5-S6).

4 | DISCUSSION

4.1 | Trajectories of acute otitis media in childhood

This study is the first to reveal three distinct trajectories of AOM in childhood: not being prone to it, indeed being prone to it and being prone to it only in the first 3 years of life. We found that gender and day care, which have previously been described in association with childhood AOM, in our studied population were associated only with membership of the early-AOM trajectory. This strengthens the idea that children in this subgroup perhaps have a different phenotype from children who remain AOM-prone.

4.2 | Gender

Male gender generally is associated with increased odds of acquiring AOM in childhood.^{2,12,17,18} The present study shows increased odds of AOM among boys only in the early-AOM subgroup. Recent studies among subjects below 12, 18 and 24 months showed a similar negative association among boys, with OR 2.6, 1.3 and 1.8, respectively.^{2,6,18} Several studies among older subjects described no significant difference between boys and girls aged from 3 to 16 years.^{19,20} These findings suggest that gender may perhaps serve as a predictor for AOM in the first years of life, but not beyond the age of three years.

TABLE 1 Characteristics of children and their mothers based on imputed data

Characteristic	Non-otitis prone	Early AOM	Persistent AOM	Total study population
Children				
No.	3067	1335	1452	5854
Gender, n (%)				
Male	1477 (48.2)	719 (53.9)	724 (49.9)	2920 (49.9)
Female	1590 (51.8)	616 (46.1)	728 (50.1)	2934 (50.1)
Birthweight for gestational age, SDS	-0.06	0.01	-0.02	-0.03
Ethnicity				
Western	2226 (72.6)	976 (73.1)	1041 (71.7)	4242 (72.5)
Non-Western	841 (27.4)	359 (26.9)	411 (28.3)	1612 (27.5)
Season of birth, n (%)				
Spring	712 (23.2)	349 (26.1)	396 (27.3)	1457 (24.9)
Summer	849 (27.7)	334 (25.0)	348 (24.0)	1531 (26.2)
Autumn	839 (27.4)	367 (27.5)	381 (26.2)	1587 (27.1)
Winter	667 (21.7)	285 (21.3)	327 (22.5)	1279 (21.8)
Breastfed at 6 months, yes (n [%])	1100 (35.9)	411 (30.8)	438 (30.2)	1949 (33.3)
Day care at 6 months, yes (n [%])	2045 (66.7)	977 (73.2)	948 (65.3)	3971 (67.8)
Pet in household, yes (n [%])				
Rodent	168 (5.5)	69 (5.2)	60 (4.1)	298 (5.1)
Dog	238 (7.8)	94 (7.0)	128 (8.8)	459 (7.8)
Bird	82 (2.7)	39 (2.9)	55 (3.8)	175 (3.0)
Cat	740 (24.1)	330 (24.7)	379 (26.1)	1448 (24.7)
Mothers				
Age at intake, median (IQR)	31.1 (28.1-34.1)	31.5 (28.6-34.4)	31.2 (28.2-34.2)	31.2 (28.2-34.2)
Educational level, n (%)				
Higher	1878 (61.2)	839 (63.0)	844 (58.1)	3560 (60.8)
Lower	1189 (38.8)	496 (37.0)	608 (41.9)	2294 (39.2)
Parity, n (%)				
Nulliparous	1795 (58.5)	752 (56.3)	824 (56.7)	3370 (57.6)
Multiparous	1272 (41.5)	583 (43.7)	628 (43.3)	2484 (42.4)
Smoking during pregnancy, n (%)				
No	2388 (77.9)	1041 (78.0)	1124 (77.4)	4553 (77.8)
Yes, until pregnancy was known	275 (9.0)	131 (9.8)	118 (8.1)	524 (9.0)
Yes, continued smoking in pregnancy	404 (13.1)	163 (12.2)	210 (14.5)	777 (13.3)
Postnatal household smoking, yes (n [%])	996 (32.5)	422 (31.6)	527 (36.3)	1945 (33.2)

Note: Data after multiple imputation represent the pooled results derived from 10 imputed data sets.

4.3 | Day-care attendance

Certain environmental factors are related to an increase in viral pathogens, which in turn are associated with increased incidence of URTIs—and thus ear infections.^{8-10,21} It is well established that day-care attendance exposes a child to a higher amount of viral pathogens. Day-care attendance has indeed often been related to increased risk of AOM, with risk further increasing for children who attend day care for a longer period (>12 months).^{2,17,18,21} In the Netherlands, maternity

leave consists of 16 weeks for the mother, of which at least 12 weeks are taken after childbirth. Of our population, approximately 70% of children attended day care at the early age of 6 months, and 77.3% at 12 months. Day-care attendance rates of three-year-old children in European Union member states vary greatly from 3% to 28% of children in Iceland, Slovenia, Portugal, Poland, Italy and Denmark to 60%-70% in Austria and the Netherlands (<http://appsso.eurostat.ec.europa.eu>). A recent study in a Danish population found that children who had started day-care attendance before the age of 12 months had an

TABLE 2 Multivariate analysis of associations between determinants and membership of different childhood AOM trajectories

Determinants	Early AOM OR (95% CI) P-value	Persistent AOM OR (95% CI) P-value
Male gender	1.26 (1.11-1.43) P = 0.001	1.07 (0.94-1.21)
Aberrant birthweight for gestational age ^a	1.06 (1.00-1.13)	1.05 (0.99-1.12)
Higher maternal age ^b	1.01 (1.00-1.03)	1.01 (0.99-1.02)
Season of birth		
Spring	Ref.	Ref.
Summer	0.81 (0.65-1.01)	0.74 (0.62-0.90) P = 0.002
Autumn	0.89 (0.73-1.09)	0.82 (0.68-0.99) P = 0.04
Winter	0.89 (0.72-1.09)	0.88 (0.73-1.07)
Breastfeeding at 6 months	0.78 (0.66-0.91) P = 0.003	0.77 (0.66-0.90) P = 0.002
Day-care attendance at 6 months	1.31 (1.06-1.60) P = 0.015	0.92 (0.79-1.09)

Note: Reference category for trajectories: non-otitis-prone trajectory.

Significant ORs in bold, $P < 0.05$.

^aBelow or above 2 SD birthweight for gestational age.

^bIncrease per year of in maternal age at birth of study subject.

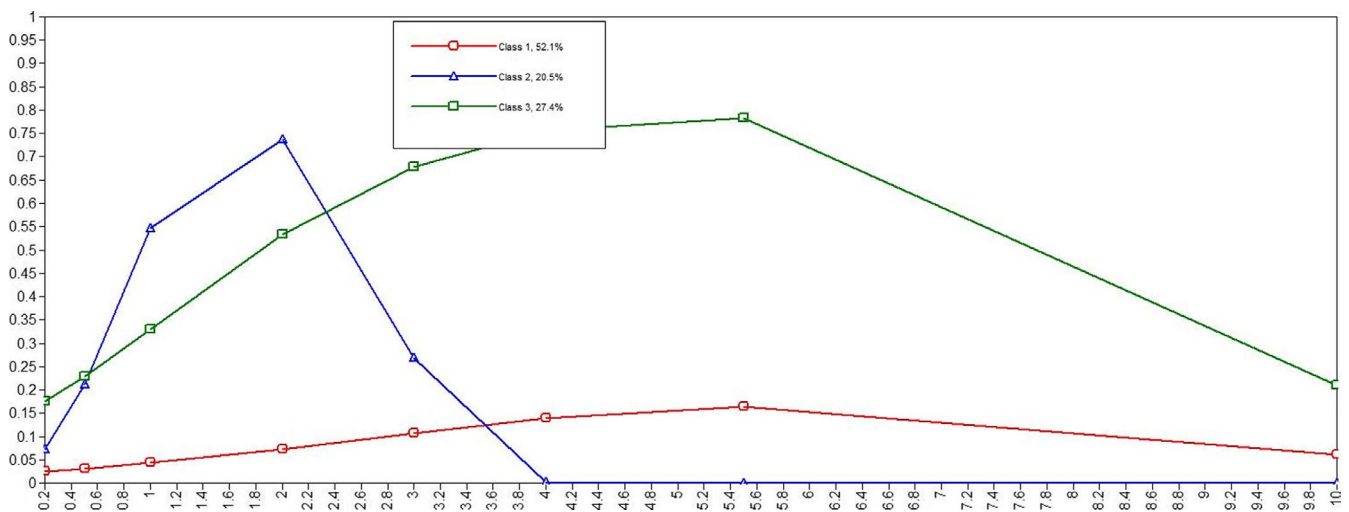


FIGURE 3 Trajectories of AOM susceptibility in childhood: The plot shows three distinct trajectories of childhood AOM, knowing the non-otitis-prone (red), early-AOM (blue) and persistent-AOM (green) trajectories

increased probability risk of experiencing more than three episodes of AOM at 18 months, and to a lesser extent at 7 years of age.⁶ These findings may explain in part why in our study the percentage of day-care attendance was highest among children prone to early AOM and that only this subgroup had increased odds of acquiring AOM.

4.4 | Breastfeeding

The positive effect of breastfeeding on AOM susceptibility is widely accepted.^{1,2,5,17} Possible explanations of this positive effect include a lower rate of URTIs through the effects of secretory IgA, cytokines and long-chain fatty acids in breast milk, which are paramount to

development of the infant's immune system.⁷ The greatest protection of breastfeeding on AOM has been described in children breastfed for at least 6 months.^{2,5} Shorter duration of breastfeeding induced higher AOM rates, both below 2 years of age and later in childhood.^{6,20,21} This is in concurrence with findings in our studied population, where breastfeeding at 6 months was associated with decreased odds of acquiring AOM in both the early- and persistent-AOM trajectories.

4.5 | Season of birth

Season of birth may be associated with either an increase or decrease in the rate of URTIs, depending on the season. This study

found a beneficial effect of being born in the summer and autumn as compared to being born in the spring in the persistent-AOM trajectory, yet interpreting this result is difficult. Literature on the possible relationship between AOM and season of birth is contradictory; some studies report that birth in the autumn would carry higher odds of AOM, whereas other studies report lower AOM rates among subjects born in the autumn.^{9,10,22} Moreover, definitions of seasons vary across countries, which limits generalisability of these results.

4.6 | Strengths and limitations

This study has several strengths and weaknesses inherent to its design. A strength lies in its large population-based study sample with repeated measurements and extensive data on determinants. Medical records or otoscopy was not available in our data set. Outcome was parent-reported which holds the risk of introducing recall bias. An episode of AOM is often a painful experience for a young child, one that parents may not easily forget. The diagnostic value of parent-reported earache, fever and otorrhoea in AOM was shown previously with a sensitivity and specificity of 71% and 80%, respectively.²³ Yet, in other studies specific symptoms such as ear tugging/rubbing and restless sleep were not significantly associated with occurrence of AOM.²⁴ A further limitation of this study is that it lacked data on surgical history pertaining adenoidectomy or insertion of ventilation tubes. Still, in our experience even after ventilation tube insertion the otitis-prone child will likely go through episodes of (mild) otorrhoea after URTIs or swimming. To check for possible non-response bias, we compared characteristics of children lost to follow-up with those of the studied population. The characteristics compared well between these groups, supporting that non-response values are missing at random (Table S7). A further limitation was that data on vaccination status—a possible intermediate—were not available in this study. The Netherlands national immunisation programme was established in 1957 and currently holds coverage of > 95% of all Dutch children (<http://www.rivm.nl/en>). The most frequently involved bacterial pathogens in AOM are *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*. Widespread use of pneumococcal conjugate vaccines (PCVs) has decreased incidence of AOM since its introduction. It has been shown that PCVs can prevent early episodes of disease associated with vaccine serotypes, resulting in a reduction of subsequent complex cases caused by non-vaccine serotypes and other otopathogens, which contribute considerably to the disease burden.²⁵ PCV-7 was introduced in the Netherlands immunisation programme in June 2006, shortly after inclusion of subjects in this study had been completed. It is likely that many subjects in our data set were subsequently vaccinated.

Our analyses provide information on altered odds of acquiring AOM within a specific trajectory. As such, results of this study cannot be extrapolated to form a prediction model. We trust that results from this study still contribute to the understanding of the complex aetiology of childhood AOM and that increased knowledge of its

aetiology will ultimately lead to earlier identification of otitis-prone children.

5 | CONCLUSION

Half of all AOM-prone children in the studied population recovered after the age of 3 years. Future research is needed to better predict which child will remain otitis-prone and which recovers after 3 years of age. In this way, appropriate clinical intervention could be better tailored towards the needs of the individual child.

6 | IRB STATEMENT

The study has been approved by the Medical Ethics Review Board of the Erasmus University Medical Center in Rotterdam, the Netherlands (MEC-2007-413-NL21545.078).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Dr Van Ingen conceptualised and designed the study, performed the statistical analyses and drafted the manuscript; Dr Le Clercq assisted in conceptualising and designing the study, assisted in data collection and supervised the statistical analyses; Dr Jaddoe initiated and designed the Generation R Study, supervised data collection for the Generation R Study and reviewed the manuscript; Dr Moll contributed to the original data collection of the Generation R Study and reviewed the manuscript for intellectual content; Dr Duijts provided comments and consultation regarding statistical analyses and the manuscript; Dr Raat made important contributions to the design of the Generation R study and reviewed the manuscript for important intellectual content; Dr Baatenburg de Jong critically revised the manuscript and was responsible for the infrastructure of the study; and Dr Van der Schroeff assisted in conceptualising and designing the study, supervised analyses and drafting of the manuscript. All authors approved the final manuscript as submitted.

DATA AVAILABILITY STATEMENT

The data are available from the corresponding authors upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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