

Acute Otitis Media During Infancy

Parent-reported Incidence and Modifiable Risk Factors

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Background: Age at exposure to acute otitis media (AOM) risk factors such as day care attendance, lack of breastfeeding and tobacco smoke is little studied but important for targeting AOM prevention strategies. Moreover, studies are typically restricted to clinically diagnosed AOM, while a significant subset can occur outside the health care system, depending on the country setting. This study aims to determine risk factor exposure and effect of its timing within the first year of life on parent-reported AOM symptom episodes.

Methods: In the Wheezing and Illnesses Study Leidsche Rijn birth-cohort study, 1056 children were prospectively followed during their first year of life. Group day care attendance, breastfeeding and tobacco smoke exposure were recorded monthly and parent-reported AOM symptoms daily. Generalized estimating equations were used to estimate the association between the time-varying risk factors and AOM symptom episodes, while correcting for confounding by indication.

Results: The first-year incidence rate of parent-reported AOM was 569/1000 child-years [95% confidence interval (CI): 523–618]. Children who attended day care had higher odds of developing AOM symptom episodes compared with those not attending (odds ratio: 5.0; 95% CI: 2.6–9.6). Tobacco smoke exposure and (a history of) breastfeeding were not associated with AOM. Test for interaction revealed that the effect of day care increased with each month younger in age.

Conclusions: First-year day care attendance is a major risk factor for AOM symptom episodes among infants in the community. This adjusted effect estimate is higher than previously reported and is age-dependent. AOM prevention strategies in day care facilities should therefore focus in particular on the youngest age groups.

Key Words: acute otitis media, day care, cohort study

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Acute otitis media (AOM) is a common infection during infancy. By the age of 1 year, 25%–36% of children have experienced at least 1 episode of AOM and approximately 20% of children develop recurrent AOM.^{1–7} AOM is one of the main reasons for primary care visits, specialist referral, antibiotic consumption and surgical ear,

nose and throat procedures among young children.^{6–9} But besides the high burden on health care, AOM also poses a high burden on parents and families; during an episode of AOM, which lasts on average 6–9 days, most parents are absent from work for 2–3 days and experience reduced quality of life because of lack of sleep and concerns about their child's health.^{10,11} For these reasons, prevention of AOM is of major public health and economic importance.^{6,7,10–14}

An important focus of AOM prevention is identification of preventable risk factors and subsequent minimization of exposure. Established and potentially modifiable risk factors include day care attendance, lack of breastfeeding and exposure to tobacco smoke.^{3,4,15–19} To optimize preventive efforts, knowledge on the critical timing of these exposures is required, but this has been very little studied thus far.

Studies on AOM risk factors have typically focused on physician-diagnosed AOM, while it is estimated that in The Netherlands, no health care is sought for 30%–50% of AOM episodes in young children.^{7,20} Therefore, targets for prevention preferably address modifiable risk factors related to AOM in the community, rather than in a subset of infants visiting primary care for AOM symptoms. Also, the effect of the timing of these risk factors on the occurrence of AOM has been poorly described thus far, making it difficult to determine the optimal timing for interventions targeted at preventing AOM.

With this study, we aim to determine the impact of day care attendance, breastfeeding and tobacco smoke and the effect of timing of these risk factors in the first year of life on the occurrence of AOM symptom episodes. To capture both medically and non-medically attended AOM symptom episodes, we investigated the association between these risk factors and parent-reported AOM symptom episode occurrence in the community in a cohort of Dutch infants.

MATERIALS AND METHODS

Wheezing and Illnesses Study Leidsche Rijn (WHISTLER) Cohort Study

This study was performed as part of the WHISTLER, a prospective birth-cohort study on perinatal and infant risk factors for wheezing illness. WHISTLER enrolled healthy newborns born between December 2001 and December 2012 living in the Leidsche Rijn district of Utrecht, The Netherlands. Study design and rationale of WHISTLER are described in detail elsewhere.²¹ In short, parents were invited by telephone to participate within 2 months after birth. Infants with major congenital abnormalities, neonatal respiratory disease or a gestational age of less than 36 weeks were excluded from the study.²¹

Data Collection

At baseline, at approximately 6 weeks of age, parents filled in questionnaires about family and socioeconomic characteristics, pregnancy, the child's perinatal period and general health. Parents

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were asked to record daily respiratory symptoms of their newborn child on monthly distributed diary sheets up to the age of 12 months. Additionally, parents were asked monthly whether the child visited a day care center, was exclusively breastfed and exposed to tobacco smoke.²¹ From April 2008 onwards, the daily symptom recording was extended to include otorrhoea and otalgia. Children with at least 6 completed monthly questionnaires asking for otorrhoea and otalgia were included in our study. Therefore, we used data from children participating in WHISTLER between October 2007 and December 2012. The WHISTLER study was approved by the medical ethics committee of the University Medical Centre Utrecht. Written informed consent was given by all participating parents.²¹

Definition of Outcome Variable

The primary outcome variable for this study was parent-reported AOM symptom episodes (no episode vs. 1 or more episodes) during the 12-month follow-up. An AOM symptom episode was defined as parent-reported fever with otorrhoea and/or otalgia occurring on the same day. If 2 consecutive episodes were separated by at least 7 days without any of these symptoms present, the second episode was recorded as a new episode.

Definition of Risk Factors and Confounders

The risk factors of interest were day care attendance, exclusive breastfeeding and pre- and postnatal tobacco smoke in the first year of life. Day care attendance was defined as visiting a group day care center for at least one-half day each week. Day care attendance was defined as a time-varying variable and was determined for each month of age separately, categorized as follows: (1) day care attendance in the first year of life but not yet in the current month (reference group); (2) day care attendance in the current month; (3) day care attendance in the past and (4) no day care attendance during any of the months in the first year of life. The distinction between the categories “day care attendance in the first year of life but not yet in the current month” and “no day care attendance during any of the months in the first year of life” was made because we hypothesized that children who never go to day care may be different from those attending day care and consequently do not have comparable background risk profiles for AOM. For example, when children are seen as fragile or unhealthy by their parents, parents may decide not to send their children to day care. Such differences could result in confounding by indication if not adjusted for.

Also, exclusive breastfeeding was defined as a time-varying exposure for each month of age separately. Breastfeeding was categorized as follows: (1) never received exclusive breastfeeding (reference); (2) received exclusive breastfeeding during the current month and (3) received exclusive breastfeeding in the past. The second category was used to determine the direct effect of breastfeeding, whereas the third category was used to determine whether a history of breastfeeding reduced the odds of developing parent-reported AOM symptom episodes.

Prenatal exposure to tobacco smoke (yes/no) was defined as maternal smoking of ≥ 1 cigarette(s) a day during pregnancy or exposure to environmental smoke for ≥ 2 hours a week during pregnancy.^{22,23} Postnatal exposure to tobacco smoke (yes/no) was considered present when the child was exposed to tobacco smoke in the residential home or elsewhere for at least one part of the day per week.^{22,23}

Gender, parental educational level as an indicator for socioeconomic status, age (months), a positive family history of asthma and the presence of older siblings were considered confounders. Educational level was defined as high when one or both parents completed university or higher vocational education and as low-middle when both parents completed high/intermediate/low

secondary education or had no formal education.^{23,24} A family history of asthma was defined as present when at least 1 parent had family physician-diagnosed asthma and symptoms of this illness in the last 12 months.²³

Statistical Analysis

Descriptive statistics were used to assess characteristics of the study population and the occurrence of parent-reported AOM symptom episodes. The incidence of AOM symptom episodes per 1000 child-years was calculated by dividing the number of parent-reported AOM symptom episodes by the total number of child-years of observation. Baseline characteristics of children according to first-year occurrence of AOM were compared using χ^2 tests.

To assess the association between the risk factors and occurrence of parent-reported AOM symptom episodes, generalized estimating equations (GEEs) with a binomial distribution were used with parameter estimates expressed as odds ratios (ORs). Day care attendance and breastfeeding were analyzed as time-varying exposures. For example, when a child started attending a day care center at 3 months of age, the first 2 months were assigned to the category “day care attendance in the first year of life but not yet in the current month,” whereas the third month was assigned to the category “day care attendance in the current month.” The GEE method takes into account the correlation between repeated measurements in the same individual.

In the GEE model, we estimated the association between each potential risk factor and the occurrence of AOM symptom episodes during the first year of life, while adjusting for adherence to follow-up (ie, the number of completed monthly questionnaires) per child, age in months, socioeconomic status, gender, siblings and a family history of asthma.

To test whether the association between day care attendance and AOM symptom episodes was dependent on age, we assessed presence of significant interaction in a separate analysis including only children who attended day care in their first year of life. For this analysis, we used a dichotomous day care variable: no current day care and current day care attendance.

The analyses were carried out with SPSS version 22 (IBM SPSS Statistics 22, Chicago, IL).

RESULTS

Study Population

Figure 1 shows the number of children included in the current study. Complete data and at least 6 months follow-up were available in 1056 of the eligible 1167 children (90.5%). Table 1

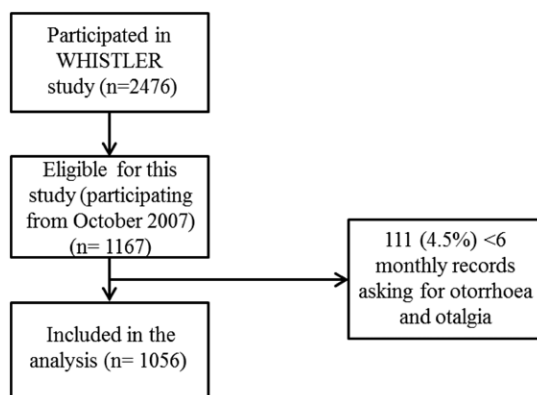


FIGURE 1. Flowchart of the study population.

TABLE 1. Characteristics of the study population

Characteristics	AOM Episode	
	No	Yes
Number of infants	710	346
Age at first episode*, mo, n (%)		
0–3	-	13 (1.2)
4–6	-	97 (9.2)
7–9	-	144 (13.6)
>9	-	92 (8.7)
Gender, n (%)		
Male	342 (48.2)	173 (50.0)
Female	368 (51.8)	173 (50.0)
Sibling(s), n (%)		
No	294 (44.9)	148 (44.6)
Yes	361 (55.1)	184 (55.4)
Parental education level, n (%)		
Low/middle	101 (15.2)	44 (13.5)
High	565 (84.8)	282 (86.5)
Exclusive breastfeeding, mo, n (%)		
No breastfeeding	134 (19.7)	64 (19.1)
0–3	266 (39.1)	140 (41.8)
>3–6	163 (24.0)	86 (25.7)
>6	117 (17.2)	45 (13.4)
Age at first daycare visit, mo, n (%)		
No daycare attendance	125 (17.9)	34 (10.0)
0–2	74 (10.6)	44 (12.9)
3–5	403 (57.8)	221 (65.0)
≥6	95 (13.6)	41 (12.1)
Prenatal exposure tobacco smoke, n (%)		
No	632 (95.9)	319 (97.6)
Yes	27 (4.1)	8 (2.4)
Postnatal exposure tobacco smoke, n (%)		
No	659 (97.8)	327 (96.7)
Yes	15 (2.2)	11 (3.3)
Family history of asthma, n (%)		
No	533 (87.1)	245 (83.1)
Yes	79 (12.9)	50 (16.9)

*Percentage of total population of included children. AOM indicates acute otitis media.

shows the baseline characteristics of the study population included in the analyses. The infants included in this analysis (n = 1056) were comparable to the infants excluded from this analysis (n = 111) with respect to gender, a family history of asthma and education level of the parents ($P > 0.05$, χ^2 test). The percentage children with an older sibling was higher in children excluded from the analysis compared with children included in the analysis, 65.4% versus 55.2%, respectively ($P = 0.047$).

Of 1056 children, 32.8% experienced at least 1 parent-reported AOM symptom episode. The mean age at which the first AOM symptom episode occurred was 7.8 months (standard deviation: 2.4). A large majority of children started day care in their first year of life (84.7%). During the 977 person-years of follow-up (median: 12 months), 556 AOM symptom episodes were recorded [AOM symptom episode incidence rate during the first year of life: 569/1000 child-years; 95% confidence interval (CI): 523–618].

Associations Between the Risk Factors and the Occurrence of AOM

Table 2 shows the ORs for the association between the time-varying risk factors and AOM symptom episodes. Current day care attendance was significantly associated with the development of AOM symptom episodes. Compared with a child of the same age not yet attending day care, a day care attendee had a 5.0 (95% CI: 2.6–9.6) higher odds of experiencing an AOM symptom episode during a particular month after additional adjustment for number of completed

TABLE 2. The Associations Between the Occurrence of AOM in the First Year of Life and Potential Risk Factors

Characteristics	Adjusted Model* OR (95% CI)
Exclusive breastfeeding	
Never	Ref.
Yes, current month	0.85 (0.50–1.43)
Yes, but in the past	0.98 (0.70–1.38)
Prenatal exposure tobacco smoke	
No	Ref.
Yes	0.50 (0.20–1.23)
Postnatal exposure tobacco smoke	
No	Ref.
Yes	1.58 (0.86–2.91)
Daycare attendance	
Yes, but not yet	Ref.
Yes, current month	4.99 (2.59–9.63)
Yes, but in the past	2.11 (0.62–7.19)
Never	2.20 (1.02–4.75)
Age (d)	1.01 (1.00–1.01)
Gender	
Female	Ref.
Male	0.98 (0.76–1.25)
Older sibling	
No	Ref.
Yes	1.16 (0.90–1.48)
Family history asthma	
No	Ref.
Yes	1.39 (0.99–1.95)
Parental educational level	
Low-middle	Ref.
High	0.89 (0.58–1.36)

*Additionally adjusted for number of completed monthly questionnaires. Ref. indicates reference.

monthly questionnaires, socioeconomic status, gender, siblings and family history of asthma. A history of day care attendance did not appear to have an effect on AOM symptom episode occurrence during subsequent months (adjusted OR: 2.1; 95% CI: 0.6–7.2) indicating the effect was of short duration. In the analysis adjusting for age, children who did not attend day care in the first year of life had 2.2 (95% CI: 1.0–4.8) higher odds of developing an AOM symptom episode compared with children not yet attending day care, suggesting children exclusively cared for at home comprise a subgroup with differential AOM rates. No significant associations were found between the occurrence of AOM symptom episodes and current exclusive breastfeeding or a history of breastfeeding. Similarly, no effect was observed for pre- or postnatal tobacco smoke exposure.

Interactions With Age

Test for interaction revealed that the association between day care attendance and the occurrence of AOM symptom episodes in the first year of life was age-dependent (OR: 1.2; 95% CI: 1.1–1.4; $P < 0.001$). With each month decrease in age during the first year of life, the OR for daycare increased by 22%. Figure 2 illustrates the OR for day care at different ages. The OR for day care was highest at 3 months of age.

DISCUSSION

This study confirms that day care attendance in the first year of life is a major risk factor for the occurrence of AOM symptom episodes in the community. More importantly, the effect of daycare on AOM symptom episodes appears to increase substantially with younger age at entry. Effects are most pronounced for children in day care as early as 3 months of age, whereas by the time children

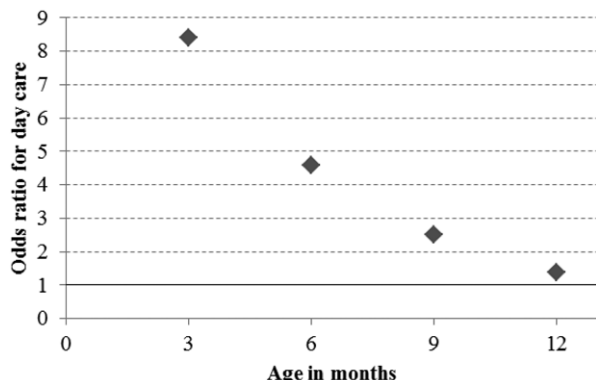


FIGURE 2. The adjusted ORs for daycare and its interaction with age in the first year of life for the occurrence of AOM symptom episodes in children who attend daycare in their first year of life (no daycare as the reference group).

are 12 months old, effects approach the null value. Our study could not confirm the protective effect of breastfeeding or the harmful effect of tobacco smoke exposure.^{4,16–19,25}

Some limitations have to be discussed. First, 28.3% of the parents did not complete all diaries on respiratory symptoms. Missing diaries may have led to an underestimation of incidence of AOM symptom episodes and the association between the studied risk factors and AOM symptom episodes in the community. By including only children with at least 6 months of information on AOM symptoms and using longitudinal analysis techniques, the risk of this misclassification bias due to missing data was minimized. Second, some potentially important environmental risk factors could not be investigated in this study, for instance, use of a pacifier, a family history of AOM episodes, type of day care facility or group size and whether a sibling attended day care.^{3,4,18,19} Third, the current study could not show an effect of breastfeeding on the occurrence of parent-reported AOM symptom episodes. To rule out any effects that were missed because of restrictions in our classification of breastfeeding, we tested an alternative classification of breastfeeding, where previous months of breastfeeding were counted as cumulative exposure for the current months, rather than a dichotomous variable for breastfeeding. This did however not change our findings of no effect of breastfeeding. Similarly, no effect of tobacco smoke exposure was found; this might be explained by the low number of children exposed to tobacco smoke in this study, limiting statistical power.

This study reported an incidence of 569 AOM symptom episodes in the community per 1000 child-years during an era where pneumococcal conjugate vaccine and *Haemophilus influenzae* type b vaccine, 2 major pathogens in AOM, are routinely administered to infants as part of the Dutch national immunization programme.^{26,27} This estimate is about 2-fold higher than the incidence of physician-diagnosed AOM episodes in the same and other European cohorts in the post pneumococcal and *Haemophilus influenzae* type b vaccine era.^{20,28,29} Importantly, a previous study from our group demonstrated that AOM symptom episodes for which no health care is sought differ only in their duration of symptoms (2 days less), but are comparable in symptoms otherwise to health care-attended AOM.²⁰ This illustrates that physician-diagnosed AOM alone does not provide a comprehensive estimate of AOM burden among young infants in the community, at least not in countries where health-seeking behavior is comparable to the Netherlands.

Most studies investigating risk factors associated with the occurrence of AOM episodes in children relied on physician-diagnosed AOM episodes.^{3,4,15–18,30,31} A small number of studies used

parent-reported AOM episodes as an outcome, but those episodes were recorded retrospectively.^{32–35} This study investigated prospectively the associations between risk factors and parent-reported AOM symptom episodes, which included both physician- and nonphysician-diagnosed episodes. Although we cannot rule out some misclassification, parent-reported AOM reflects the community burden of AOM symptom episodes comprehensively and is therefore an important measure of public health interest. Also, because of the high frequency of follow-up measurements, every day for respiratory and otitis symptoms and every month for day care attendance, breastfeeding and postnatal exposure to tobacco smoke, we minimized recall bias in this study.

Day care attendance was found to be a major risk factor for AOM symptom episodes in the current study with an OR as high as 5.0. Other studies have generally reported weaker associations between day care attendance and AOM, varying between 1.3 and 4.7.^{3,4,19,36–39} The difference between the ORs reported in previous studies and the current study might be explained by incomplete adjustment for confounding by indication in other studies. In our study, we examined how the children who never attended day care were different in their background AOM risk. It appeared that they had a 2.2 higher odds for AOM symptom episodes, compared with those equally unexposed to daycare, but with future day care attendance. Such differences can cause confounding by indication and can result in underestimation of the true effect of daycare on AOM symptom episode occurrence, if not properly adjusted for.

Our study also showed significant interaction between day care attendance and age, indicating that the effect of day care increases by 22% for each month younger age. In the Netherlands, a relatively high number of children start day care as early as before 3 months of age (11.4%) in our study marking the end of maternity leave; this might be another explanation for the high effect size of day care compared with previous studies. These findings indicate that the attendance of day care by very young children results in a substantial increased AOM burden in young children. Another study using data from the WHISTLER study combined with family physician data from the participants has shown that first-year day care attendance was also associated with higher AOM-related health care costs.⁴⁰

In conclusion, this study shows that first-year day care attendance is a major risk factor for the occurrence of AOM symptom episodes among infants in the community, which strongly interacts with age. AOM prevention strategies in day care facilities should therefore focus in particular on the youngest age groups, for instance by reducing group sizes.^{3,37} Alternatively, postponing day care until later age could reduce AOM symptom burden substantially and counselling parents on these effects should be considered. Future studies should focus on the long-term impact of early day care attendance on consequently early AOM on disease burden in the community.

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