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Factors associated with the development of paediatric chronic otitis media by age nine: a prospective longitudinal cohort study of 6560 children

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Main Article

Mr P J Clamp takes responsibility for the integrity of the content of the paper

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Abstract

Objective. This study aimed to analyse social, health and environmental factors associated with the development of chronic otitis media by age nine.

Method. This was a prospective, longitudinal, birth cohort study of 6560 children, reviewed at age nine. Chronic otitis media defined as previous surgical history or video-otoscopic changes of tympanic membrane retraction, perforation or cholesteatoma. Non-affected children were used as the control group.

Results. Univariate analysis demonstrated an association between chronic otitis media and otorrhoea, snoring, grommet insertion, adenoidectomy, tonsillectomy, hearing loss, abnormal tympanograms and preterm birth. Multivariate analysis suggests many of these factors may be interrelated.

Conclusion. The association between chronic otitis media and otorrhoea, abnormal tympanograms and grommets supports the role of the Eustachian tube and otitis media (with effusion or acute) in the pathogenesis of chronic otitis media. The role of snoring, adenoidectomy and tonsillectomy is unclear. Associations suggested by previous studies (sex, socioeconomic group, parental smoking, maternal education, childcare, crowding and siblings) were not found to be significant predictors in this analysis.

Introduction

Otitis media is a broad term used to describe an inflammatory process within the middle-ear cleft. Otitis media, in all its forms, represents a major worldwide health burden.[1] Chronic otitis media is characterised by more long-term changes to the shape and function of the eardrum, including tympanic membrane retraction, perforation and cholesteatoma. Chronic otitis media is a leading cause of permanent hearing loss, especially within developing countries.[2–4] It is associated with reduced quality of life and may require complex ear surgery to remove diseased tissue and preserve or reconstruct hearing function. The diagnosis of chronic otitis media increases the risk of serious and potentially life-threatening complications including mastoiditis, meningitis, intracranial venous sinus thrombosis and intracranial abscess formation.[5]

Although acute otitis media and otitis media with effusion (OME) are common in childhood, chronic otitis media is relatively rare[1]. In the UK, the prevalence of active and inactive middle-ear disease in British adults is around 1.5 per cent and 2.6 per cent, respectively.[6] It is unclear why some children with a propensity for acute otitis media or OME progress to chronic otitis media, whereas others do not. Numerous studies have attempted to identify risk factors for chronic otitis media.[6–18] These are usually case-control studies based on single-point observational studies of affected groups. To date, there have been limited, prospectively collected population studies of the risk factors for chronic otitis media in children.[9,19]

The Avon Longitudinal Study of Parents and Children is a unique, prospective UK birth cohort study following the health and development of over 14 000 children from before birth. As part of the study, some children underwent video-otoscopic examination of their tympanic membranes at nine years of age. A previous study has reviewed these images and reported on the prevalence of chronic otitis media changes including tympanic membrane retraction, perforation and undiagnosed cholesteatoma.[20] Retraction of the tympanic membrane pars flaccida and pars tensa was seen in 9.6 per cent and 7.9 per cent of cases, respectively. There were 15 cases of suspected cholesteatoma.

The aim of this study was to identify associations and potential risk factors for the development of paediatric chronic otitis media at age nine. The prospective cohort design allowed factors associated with chronic otitis media to be identified without recall bias.

Materials and methods

The Avon Longitudinal Study of Parents and Children

The Avon Longitudinal Study of Parents and Children or 'Children of the 90s study' recruited 14 541 pregnant mothers resident in a defined area (Avon in the southwest of the UK) with an expected date of delivery between 1st April 1991 and 31st December 1992. This prospective, ethically approved, longitudinal birth cohort study collected health, social, environmental and genetic data for the families and children enrolled. Mothers and their children were followed up using a variety of methods including self-completion questionnaires and direct examination.[21] The Avon Longitudinal Study of Parents and Children website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

Ethical approval for this study was granted by The Avon Longitudinal Study of Parents and Children Ethics and Law Committee and the Local Research Ethics Committees.

Study sample

The study sample consisted of children within The Avon Longitudinal Study of Parents and Children who attended a nine-year-old child review 'focus clinic' with video-otoscopic data available. Children with a history of cleft lip or palate were excluded. A cleft lip or palate is known to be a strong independent risk factor for the development of chronic otitis media, and further analysis of the associations and risk factors for these children was deemed unlikely to be informative.[22,23]

Outcome data

Chronic otitis media

At the 9-year-old child focus clinic, data collected included video-otoscopic imaging of the child's tympanic membrane and a parental interview regarding the child's ENT surgical history. This study utilises the method of obtaining, coding and staging the tympanic membrane images described in a previous paper.[20] For the purposes of this study, chronic otitis media was defined and categorised as: (1) significant chronic otitis media: video-otoscopic evidence of stage two retraction of the pars tensa or flacida, perforation, cholesteatoma or attic crust, or history of surgery for cholesteatoma or perforation; (2) mild chronic otitis media: video-otoscopic evidence of stage one retraction of the pars tensa or flaccida; or (3) no chronic otitis media: video-otoscopic evidence of normal tympanic membrane, with or without middle ear effusion, ventilation tube or tympanosclerosis.

Where an image of the tympanic membrane was available for one ear only, the outcome for that child was categorised according to that ear only. This was deemed appropriate because for those children with data for both ears available, if no chronic otitis media was recorded in one ear, 94 per cent of those children also had no chronic otitis media recorded in the other ear. This system of classification is consistent with previous classification systems used for chronic otitis media.[24]

ENT and hearing factors

Information on the child's ENT symptoms was collected by maternal questionnaire at ages 6, 18, 30, 42, 57, 69, 81, 91 and 103 months. Symptoms reported at each time point included: pus or mucus (not wax) leaking from ears, a cough for at least two days, having a fever with a cough, snoring for more than a minute at a time, and breath holding while asleep.

The following variables were derived from the longitudinal questionnaire data: ear pus or mucus leakage, breath holding and snoring, early snoring, prolonged snoring, cough count, and fever with a cough. All of these variables are defined in more detail in the relevant table legend.

At the nine-year-old child focus clinic, information was gathered about the child's history of ENT surgery including: ear surgery for chronic otitis media, insertion of grommets (categorised as none, once or more than once), history of adenoidectomy and history of tonsillectomy.

Information about the child's hearing and middle-ear function were available from the seven-year-old child focus clinic.

Child, maternal and socioeconomic factors

Smoking in pregnancy information was obtained from maternal questionnaires at 18- and 32-weeks gestational age. A variable of any smoking in pregnancy was derived. The birthweight and gestational age of the child (categorised as less than 37 weeks or 37 weeks or more) were obtained from the maternity records. Information on the mother's highest education level, the mother's age when the child was born and the parents' occupation were all collected during pregnancy. Definitions for these variables can be seen in Table 1. Child factors included the sex of the child and ethnicity, categorised as white or non-white.

Mothers reported how they fed their baby when the child was age 4 weeks, 6 and 15 months of age, and variables were derived for any breastfeeding up to 15 months and for the duration of breastfeeding. Information on dummy use (also known as pacifier, soother or comforter) was reported in maternal questionnaires when the child was aged 4 weeks, 6 months and 24 months. A variable of any dummy or pacifier use was derived. History of the mothers' use of grommets was obtained by parental questionnaire.

Additional medical factors

Information on allergy was obtained using the skin prick test responses carried out at the age seven focus clinic.[25] Atopic dermatitis was measured according to the International Study of Asthma and Allergies in Childhood 1994 protocol at the seven-year-old focus clinic.[26–28] A diagnosis of asthma by a doctor was obtained from maternal questionnaires when the child was age 91 months. All variables relating to medical factors are defined in the relevant table legends.

Environmental factors

Information about day care was available from parent questionnaires at age 15, 24 and 38 months. A variable was derived of regular day care at any time up to 38 months; any day care up to 38 months and day care of more than 10 hours per week at 38 months.

Information about household crowding was obtained when the child was age 8, 33 and 81 months. Parents were asked about the number of people living in the household (including the number of children) and the number of rooms, and the crowding index was calculated. Parents provided information about damp and mould in the home when the child was aged eight months. At 6, 38 and 54 months, parents reported on the child's exposure to smoking and a variable was derived of any exposure to smoke.

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Table 1. Demographics data of the study sample*

Parameter	Original data (*n* (% or SD))†	Original plus imputed data (*n* (% or SE))†
Sex of child		
– Male	3251 (50)	3251 (50)
– Female	3309 (50)	3309 (50)
– Missing	0	
Child's ethnic background		
– White	5655 (96)	6281 (96)
– Non-white	230 (4)	279 (4)
– Missing	675	
Parental social class‡ (social class of the most advantaged parent)		
– I (professional)	897 (16)	958 (15)
– II	2597 (45)	2861 (44)
– III (non-manual)	1388 (24)	1598 (24)
– III (manual)	581 (10)	717 (11)
– IV (partly skilled)	220 (4)	277 (4)
– V (unskilled)	31 (<1)	149 (2)
– Missing	846	
Mother's highest education qualification		
– Certificate of Secondary Education (lowest)	605 (11)	779 (12)
– Vocational	515 (9)	621 (9)
– O-level (medium)	2068 (36)	2357 (36)
– A-level	1618 (28)	1752 (27)
– Degree (highest)	970 (17)	1051 (16)
– Missing	784	
Age of mother at birth (years)		
– Mean	29 (SD 4.6)	29 (SE 0.07)
– Range	15–44	15–44
– Missing	349	

Certificate of Secondary Education and vocational education was finished at less than 16 years of age, O-level education was up to 16 years, and A-level and degree level education was up to or more than 18 years. *Total $n = 6560$; †unless otherwise stated; ‡the parents' social class was based on the Standard Occupational Classification (1990) of the mother or partner's occupation (whichever was the more advantaged) at 32 weeks of pregnancy.[29] This was measured using the parents' occupation and based on a scale of I (professional), II, III (divided into manual and non-manual), IV (partly-skilled occupations) and V (unskilled occupations). SD = standard deviation; SE = standard error

Statistical analysis

Missing data were imputed for the study sample. Multiple imputation was used to impute missing data for all variables of interest. Five imputations were used with 50 iterations.

Little's missing completely at random ('MCAR') test indicated that the data was not missing at random ($p < 0.001$). Data was imputed, but for robustness we also completed all analysis on only the original dataset. This analysis confirms that imputing missing data did not significantly alter the results. This suggests the results are robust, irrespective of missing data.

Categorical data were analysed using the chi-square test and logistic regression. Continuous data were compared using either a *t*-test or, where data were ordinal or non-normally distributed, a non-parametric alternative. The level of significance for all tests was set to $p < 0.05$. The mean and standard deviation (SD) or standard error (SE) are reported for all normally distributed data, and the median for all non-normally distributed data.

Logistic regression was undertaken where appropriate by entering all univariate predictors where $p < 0.2$ using a backward sequential approach. Odds ratios and adjusted odds ratios resulting from logistic regression were reported alongside 95 per cent confidence intervals (CIs). A fully adjusted model is also presented, where univariate predictors with a *p*-value less than 0.1 were included.

It is uncertain if 'mild chronic otitis media' changes (stage one retraction of the pars tensa or flaccida) represent temporary changes in the appearance of the tympanic membrane or reflect a milder form of chronic otitis media. For this clinical-based reason, two sets of subgroup analyses were undertaken comparing: model 1, no chronic otitis media versus mild or significant chronic otitis media; and model 2, no or mild chronic otitis media versus significant chronic otitis media.

Results

Full information on the number of Avon Longitudinal Study of Parents and Children participants can be found elsewhere.[21,29] A total of 14 062 surviving children (at one year) were recruited to the study (Figure 1). Of these, 6935 (49 per cent) children attended the Avon Longitudinal Study of Parents and Children focus clinic at age nine (Figure 1). Female children, who were white, with a higher parental social class and higher education level of the mother, were all more likely to attend a clinic visit (all $p < 0.001$).

Twenty-six parents withdrew their children from the study and 19 children had cleft palate. These cases were removed from the analysis.

During the clinic visit, chronic otitis media data (video-otoscopic imaging) could not be obtained for either ear for 330 (5 per cent) children (reasons included that the child, parent or both declined the visit, equipment availability issues and because of time constraints).[20] No difference was found in any variable between these children and those that did have data for at least one ear. Therefore, these 330 children were excluded. There were thus 6560 participants for analysis.

There were 5814 (89 per cent) participants who had no evidence of chronic otitis media. Of the remaining participants, 350 (5 per cent) were categorised with mild chronic otitis media and 396 (6 per cent) were categorised with significant chronic otitis media. Of those with significant chronic otitis media, 13 and 9 participants were categorised with significant chronic otitis media due to a clinical history of repaired tympanic membrane perforation and a history of cholesteatoma, respectively. The remaining participants were categorised from the results of video-otoscopic imaging.

Participant and parent demographics, for both the original data and the imputed plus original data, are presented in Table 1. The ratio of females to males was split evenly (Table 1). The mean age of the mother at birth was 29 (SE, 0.07) years old, ranging from 15–44 years old. ENT derived descriptive data, for both the original data and the imputed data, are presented in supplementary Table 1, and additional descriptive data are presented in supplementary Table 2 (see Tables 2 and 3 in the supplementary material, available on *The Journal of Laryngology & Otology* website).

Tables 2, 3 and 4 present the univariate comparisons which showed evidence of significant associations between children with and without chronic otitis media. Parental social class,

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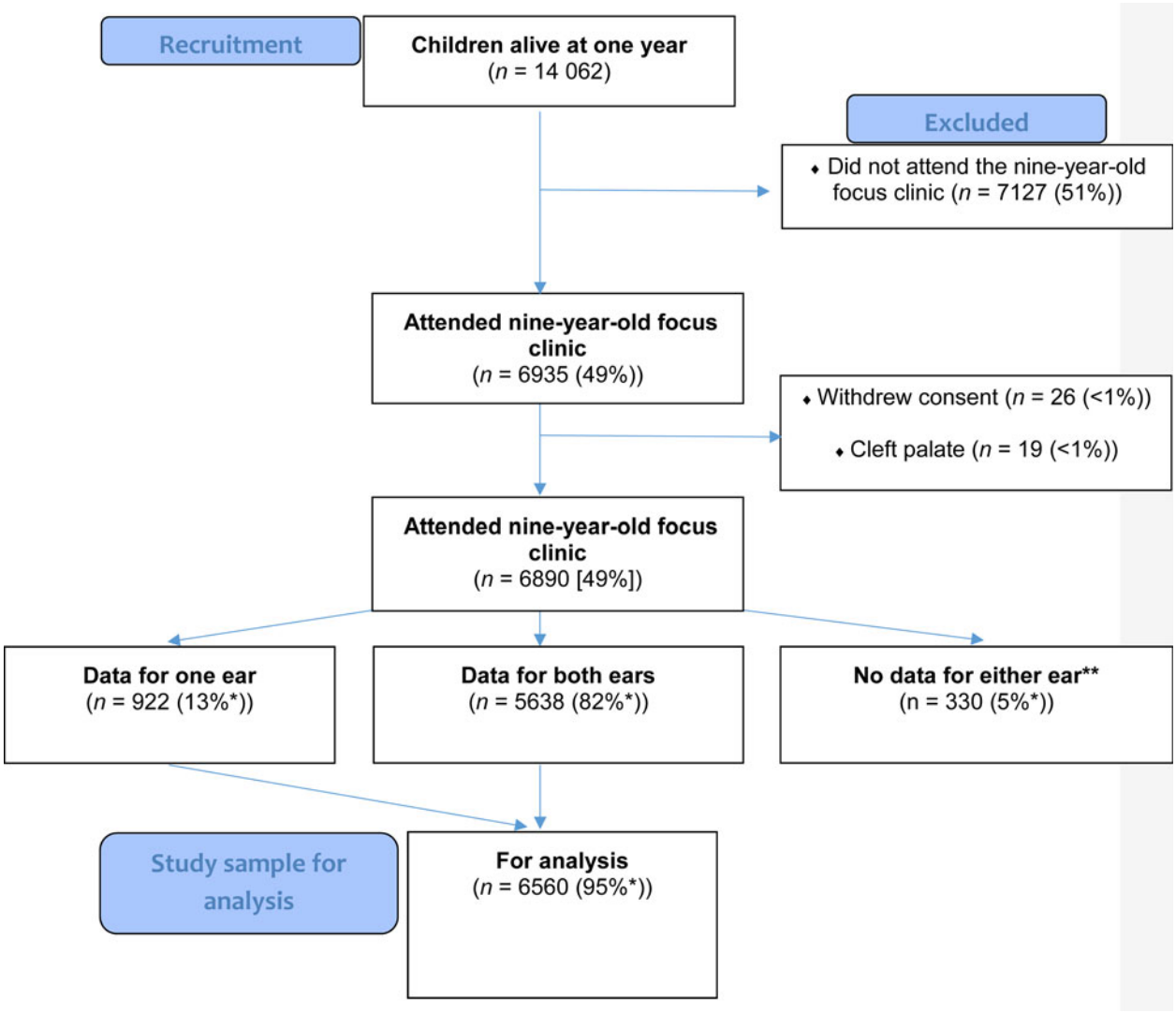

Fig. 1. Study flow chart. *Percentage of those who attended a clinic visit. **There were no significant differences in demographic data between those participants who had ear data and those that did not: gender ($p = 0.827$), ethnic background ($p = 0.655$), social class ($p = 0.942$) and mother's highest education level ($p = 0.759$).

sex of the child and maternal educational level were not associated with the presence of chronic otitis media. Age of the mother at birth was associated with the presence of chronic otitis media (only when examined as a continuous variable) although the mean difference between outcome groups was small (0.4 and 0.6 years for model 1 and 2, respectively; Table 2). A number of ENT variables showed increasing evidence of being significant univariate predictors of chronic otitis media. These included a history of pus from the child's ear, snoring, previous grommet insertion, adenoidectomy, tonsillectomy, type B or C tympanograms, and hearing loss at age seven (Table 3).

For the majority of additional variables, there was no strong evidence of an association with chronic otitis media (Table 4), with the exception of lower birthweight and earlier gestational age at birth. Allergy, asthma, attendance at day care, crowding, parental smoking, number of siblings and use of dummy or pacifier were not associated with presence of chronic otitis media (Table 4).

Multivariate models are presented in Tables 5 and 6. For both models, significant independent predictors included an early history of pus or mucus, a history of grommet insertion and a gestational age less than 37 weeks. Type B or C tympanometric recordings at age seven were also an independent predictor of chronic otitis media (Tables 5 and 6).

The fully adjusted model for no chronic otitis media versus mild chronic otitis media or significant chronic otitis media (all factors with a univariate $p < 0.01$) is presented in supplementary Table 3 (see Table 3 in the supplementary material, available on *The Journal of Laryngology & Otology* website). It can be seen that the models and odds ratios remain very similar to the independent model, implying that the models are stable and robust.

Discussion

To the authors' knowledge, this is the largest prospectively collected cohort study examining a wide range of social and health factors associated with the development of chronic otitis media in children by the age of nine.

A comparison of results from the two-analysis models demonstrates that the group with mild chronic otitis media had a profile more similar to the no chronic otitis media group. The fact that children with mild chronic otitis media share more traits with the no chronic otitis media group suggests that mild retraction of the tympanic membrane may be a transient change and that progression to more significant chronic otitis media is not inevitable. This may have implications for the clinical assessment and management of early tympanic membrane retraction in the

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Table 2. Univariate comparisons of demographics data with the outcome variable*

Parameter	No COM† (*n* (%))	Mild COM‡ (*n* (%))	Significant COM** (*n* (%))	No *vs* mild or significant COM (*p*-value (OR or MD (95% CI))	No or mild *vs* significant COM (*p*-value (OR or MD (95% CI))
Sex of child					
– Male	2894 (50)	171 (49)	186 (47)	0.323 (1.1 (0.9–1.3))	0.288 (1.1 (0.9–1.4))
– Female	2920 (50)	179 (51)	210 (53)		
Child's ethnic background					
– White	5563 (96)	335 (96)	383 (97)	0.535 (0.8 (0.5–1.5))	0.409 (0.7 (0.4–1.5))
– Non-white	251 (4)	15 (4)	13 (3)		
Parental social class (highest parental class of the most advantaged parent)					
– I (professional)	856 (15)	48 (14)	54 (14)	0.357	0.692
– II	2529 (43)	148 (42)	184 (46)		
– III (non-manual)	1440 (25)	82 (23)	76 (19)		
– III (manual)	625 (11)	41 (12)	51 (13)		
– IV (partly skilled)	241 (4)	20 (6)	16 (4)		
– V (unskilled)	123 (2)	11 (3)	15 (4)		
Mother's highest education qualification					
– CSE or vocational (low)	1235 (22)	79 (14)	86 (13)	0.440	0.264
– O-level (medium)	2105 (36)	125 (36)	128 (32)		
– A-level or degree (high)	2474 (27)	146 (25)	182 (31)		
Age of mother at birth (mean (SE); years)	29.0 (0.07)	28.9 (0.26)	28.4 (0.22)	0.024 (MD 0.4 (0.1–0.8))§	0.010 (MD 0.6 (0.1–1.1))§
Age of mother at birth (years)					
– ≤ 25	915 (16)	57 (16)	59 (15)	0.194	0.071
– 25–34	4190 (72)	252 (72)	303 (77)		
– ≥ 35	709 (12)	41 (12)	34 (9)		

Certificate of Secondary Education and vocational education (CSE) was finished at less than 16 years of age, O-level education was up to 16 years, and A-level or degree level education was up to or more than 18 years. Odds ratios (OR) with 95 per cent confidence intervals (CI) or mean difference (MD) with 95 per cent CI is presented as appropriate. If not significant, *p*-values only (resulting from the chi-square test) are reported for tables greater than 2 × 2. *Original plus imputed data, $n = 6560$; †$n = 5814$; ‡$n = 350$; **$n = 396$; §significant result. COM = chronic otitis media; SE = standard error

paediatric population and would support a conservative management approach unless more significant signs and symptoms of chronic otitis media become apparent.

Factors that were univariately associated with the development of chronic otitis media by the age of nine included a history of ear discharge, prolonged snoring, grommet insertion (especially multiple insertions), adenoidectomy or tonsillectomy, abnormal tympanometry (especially type B), hearing loss at age 7, low birthweight, and gestational age less than 37 weeks. Multivariate analysis of these factors shows a more refined picture. Multiple variables show a high degree of multicollinearity (both clinically and statistically). The ENT factors of a history of pus or mucus from the ears, previous grommet insertion, and type B or C tympanometry remained independent predictors of chronic otitis media after statistical adjustment. This suggests that the failure of other variables to enter the models (e.g. snoring) is probably due to mediating or confounding relationships between the ENT variables.

Although snoring, adenoidectomy and tonsillectomy are significant univariate predictors of chronic otitis media, this significance is lost in the multivariate analysis. This appears to be due to the fact that chronic otitis media is highly related to a number of other variables (pus or mucus leakage, breath holding, mother reported child having had grommets, tonsillectomy and adenoidectomy). This interrelationship is not unexpected; the link between adeno-tonsillar hypertrophy and sleep disordered breathing (snoring and obstructive sleep apnoea) in children is well established. Adeno-tonsillectomy remains the primary treatment for paediatric obstructive sleep apnoea.[30–32] A link between chronic otitis media and adenoidectomy has been proposed by previous studies. A 2010 retrospective cohort study suggested adenoidectomy may have a protective role in reducing the risk of developing paediatric chronic otitis media.[14] Our findings suggest that the adenoidectomy, tonsillectomy and nocturnal airway obstruction may have roles to play as risk factors for the development of chronic otitis media, although the pathophysiology underpinning this is unclear. Tonsillectomy and adenoidectomy were also related to whether the child had grommets inserted. This may provide further reason why they were not independent predictors of chronic otitis media during multivariate analysis. UK studies have shown that adenoidectomy at the time of grommet insertion reduces the risk of recurrent otitis media with effusion (OME).[33]

The association between chronic otitis media and abnormal tympanometry supports the concept that middle-ear pressure homeostasis and Eustachian tube function may be important in the formation of chronic otitis media. The lower odds ratio found in patients with type C1/2 compared to type B tympanograms and only a single grommet insertion compared

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Table 3. Univariate comparison of ENT questionnaire data with the outcome variable (original plus imputed data, $n = 6560$)

Reported	No COM ($n = 5814$) (n (%))	Mild COM ($n = 350$) (n (%))	Significant COM ($n = 396$) (n (%))	No *vs* mild or significant COM (p-value (OR (95% CI))	No or mild *vs* significant COM (p-value (OR (95% CI))
Pus or mucus leaking from the child's ear					
– Never	4439 (76)	207 (59)	197 (50)		
– Once	863 (14)	66 (19)	88 (22)	<0.001 (2.0 (1.6–2.4))*	<0.001 (2.2 (1.7–2.9))*
– >Once	512 (9)	77 (22)	111 (28)	<0.001 (4.0 (3.3–4.9))*	<0.001 (4.4 (3.5–5.7))*
Child holds breath for several seconds while sleeping†					
– No	4070 (70)	241 (69)	271 (68)		
– Yes	1744 (30)	109 (31)	125 (32)	0.478 (1.1 (0.9–1.3))	0.533 (1.1 (0.8–1.6))
Child ever snores†					
– No	4887 (84)	275 (79)	287 (72)		
– Yes	927 (16)	75 (21)	109 (28)	<0.001 (1.7 (1.4–2.1))*	<0.001 (2.0 (1.5–2.5))*
Child snores on at least two time points (prolonged snoring)‡					
– No	5277 (91)	302 (86)	323 (82)		
– Yes	537 (9)	48 (14)	73 (18)	<0.001 (1.9 (1.7–2.1))*	<0.001 (2.1 (1.6–2.8))*
Child snores at 6 and 18 months (early snoring)†					
– No	5347 (92)	321 (92)	355 (90)		
– Yes	467 (8)	29 (8)	41 (10)	0.286 (1.2 (0.9–1.6))	0.132 (1.3 (0.9–1.9))
Mother reported a history of having grommets inserted					
– No	5701 (98)	341 (97)	382 (96)		
– Yes	113 (2)	9 (3)	14 (4)	0.144 (1.6 (0.8–3.0))	0.097 (1.8 (0.9–3.7))
Child had grommets inserted (by age 9)					
– Did not have grommets	5634 (97)	275 (79)	288 (73)		
– Grommets inserted once	150 (3)	65 (19)	78 (20)	<0.001 (9.6 (7.5–12.2))*	<0.001 (7.4 (5.6–9.9))*
– Grommets inserted >1	30 (<1)	10 (3)	30 (8)	<0.001 (13.4 (8.3–21.9))*	<0.001 (15.5 (9.5–25.3))*
Child had tonsils removed (by age 9)					
– No	5738 (99)	332 (95)	375 (95)		
– Yes	76 (1)	18 (5)	21 (5)	<0.001 (4.1 (2.8–6.2))*	<0.001 (3.6 (2.2–5.9))*
Child had adenoids removed (by age 9)					
– No	5692 (98)	315 (90)	345 (87)		
– Yes	122 (2)	35 (10)	51 (13)	<0.001 (6.1 (4.6–8.1))*	<0.001 (5.6 (4.1–7.9))*
Cough count**					
– <50%	1764 (30)	89 (25)	123 (31)		
– ≥50%	4050 (70)	261 (75)	273 (69)	0.285 (1.1 (0.9–1.3))	0.682 (0.9 (0.8–1.2))
Fever reported alongside a cough					
– No cough reported/ never	1476 (25)	79 (23)	110 (28)	0.970	0.382
– Fever with some attacks	3263 (56)	197 (56)	222 (56)		
– Fever with every attack	1075 (18)	74 (21)	64 (16)		
Tympanometry at age 7 (better functioning ear)					
– Type A	4464 (77)	185 (53)	158 (40)		
– Type C1/C2	1037 (18)	101 (29)	118 (30)	<0.001 (3.1 (2.4–4.1))*	<0.001 (3.5 (5.6–4.8))*
– Type B	313 (5)	64 (18)	119 (30)	<0.001 (6.5 (5.1–8.3))*	<0.001 (7.8 (5.6–10.9))*
Audiometry age 7 in better hearing ear (dB)					
– <20 – ≥20	5694 (98) 120 (2)	333 (95) 17 (5)	363 (92) 33 (8)	<0.001 (3.4 (2.3–5.1))*	<0.001 (4.0 (2.6–6.2))*

Odds ratios (OR) with 95 per cent confidence intervals (CI) are presented as appropriate. If not significant, p-values only (resulting from the chi-square test) are reported for tables greater than 2 × 2. All variables are derived from longitudinal questionnaire data reported by the parent(s) when the child was 6, 18, 30, 42, 57, 69, 81, 91 and 103 months. *Significant result; †yes = a report of yes for at least one minute at least one 'yes often'/'most nights' across all time points; ‡yes = a report of snoring for at least one minute at least two reports of 'most nights' across time points; **cough count = per cent of times a cough was reported across all time points. COM = chronic otitis media

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Table 4. Univariate comparison of additional variables with the outcome variables (original plus imputed data $n = 6560$)

Data category	Parameter	No COM ($n = 5814$) (n (%))	Mild COM ($n = 350$) (n (%))	Significant COM ($n = 396$) (n (%))	No *vs* mild or significant *P*-value (OR or MD (95% CI))	No or mild *vs* significant *P*-value (OR or MD (95% CI))
Medical factors						
	Allergy* (7 years)				0.264 (0.9 (0.7–1.1))	0.384 (0.9 (0.7–1.2))
	– No	4575 (79)	282 (81)	319 (81)		
	– Yes	1239 (21)	68 (19)	77 (19)		
	Atopic dermatitis (7 years)				0.981 (1.0 (0.7–1.3))	0.786 (0.9 (0.6–1.4))
	– No	5347 (92)	320 (91)	366 (92)		
	– Yes	467 (8)	30 (9)	30 (8)		
	Doctor diagnosis of asthma (91 months)				0.703 (1.0 (0.9–1.3))	0.594 (1.1 (0.8–1.4))
	– No	4617 (79)	278 (79)	310 (78)		
	– Yes	1197 (21)	72 (21)	86 (22)		
Day care						
	Day care at any time (up to 38 months)†				0.525 (1.1 (0.9–1.3))	0.853 (1.0 (0.8–1.3))
	– None	3498 (60)	203 (58)	235 (59)		
	– Yes	2316 (40)	147 (42)	160 (41)		
	Day care regularly, (i.e. not a one off) (38 months)				0.317 (1.1 (0.9–1.3))	0.685 (1.1 (0.8–1.3))
	– No	3862 (66)	222 (63)	261 (66)		
	– Yes	1952 (34)	128 (37)	135 (34)		
	Day care 10+ hours per week (38 months)				0.671 (1.0 (0.8–1.3))	0.362 (1.2 (0.8–1.7))
	– No	1051 (18)	67 (19)	64 (16)		
	– Yes	4763 (82)	283 (81)	332 (84)		
Crowding						
	Number of other children in house (6 months)				0.261	0.848
	– 0	2613 (45)	133 (38)	180 (45)		
	– 1	2153 (37)	153 (44)	148 (37)		
	– >2	1047 (18)	65 (19)	68 (17)		
	Number of other children in house (81 months)				0.430	0.413
	– 0	606 (10)	31 (9)	36 (9)		
	– 1	3137 (54)	185 (53)	225 (57)		
	– >2	2071 (36)	134 (38)	136 (34)		
	Crowding index (8 months)‡				0.264	0.720
	– ≤0.5	911 (16)	56 (14)	54 (16)		
	– 0.5–0.75	2223 (37)	121 (36)	135 (37)		
	– 0.75–1	1890 (32)	121 (33)	150 (30)		
	– >1	788 (15)	52 (17)	58 (17)		
	Crowding index (33 months)‡		23 (7)		0.747	0.724
	– ≤0.5	1127 (19)	67 (19)	75 (19)		
	– 0.5–0.75	2185 (38)	136 (39)	153 (39)		
	– 0.75–1	2107 (36)	123 (35)	140 (35)		
	– >1	396 (7)	23 (7)	29 (7)		
	Crowding index (81 months)‡				0.720	0.382
	– ≤0.5	778 (14)	57 (14)	52 (15)		
	– 0.5–0.75	1962 (31)	117 (31)	128 (31)		
	– 0.75–1	2293 (35)	128 (38)	157 (35)		
	– >1	781 (19)	48 (18)	60 (20)		

(*Continued*)

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Table 4. (*Continued.*)

Data category	Parameter	No COM (*n* = 5814) (*n* (%))	Mild COM (*n* = 350) (*n* (%))	Significant COM (*n* = 396) (*n* (%))	No *vs* mild or significant *P*-value (OR or MD (95% CI))	No or mild *vs* significant *P*-value (OR or MD (95% CI))
	Presence of mould in the home (8 months)				0.101	0.366
	– None	4069 (70)	228 (65)	267 (67)		
	– Not serious	1274 (22)	93 (27)	90 (23)		
	– Serious	471 (8)	29 (8)	39 (10)		
	Presence of damp in the home (8 months)				0.818	0.851
	– None	2836 (49)	168 (48)	192 (48)		
	– Not serious	2585 (44)	157 (45)	175 (44)		
	– Serious	393 (7)	24 (7)	29 (7)		
Smoking						
	Child exposure to smoke (up to 54 months)**				0.424 (1.1 (0.9–1.3))	0.430 (1.1 (0.9–1.3))
	– None	3237 (56)	191 (54)	212 (54)		
	– Yes	2577 (44)	159 (45)	184 (46)		
	Child exposure to smoke (6 months)				0.756 (1.0 (0.9–1.2))	0.526 (1.1 (0.9–1.4))
	– None	3843 (66)	233 (67)	255 (64)		
	– Yes	1971 (34)	117 (33)	141 (36)		
	Child exposure to smoke (38 months)				0.484 (1.1 (0.9–1.3))	0.971 (1.0 (0.8–1.3))
	– None	3740 (64)	215 (61)	254 (64)		
	– Yes	2074 (36)	135 (39)	142 (36)		
	Child exposure to smoke (54 months)				0.126 (1.1 (1.0–1.3))	0.300 (1.1 (0.9–1.4))
	– None	3836 (66)	221 (63)	250 (63)		
	– Yes	1978 (34)	129 (37)	146 (37)		
	Maternal smoking during pregnancy (at any time)§				0.584 (0.9 (0.8–1.2))	0.526 (0.9 (0.7–1.2))
	– None	4700 (77)	284 (78)	326 (78)		
	– Yes	1114 (23)	66 (22)	70 (22)		
	Material smoking during pregnancy (up to 18 weeks)				0.775 (1.0 (0.8–1.2))	0.580 (0.9 (0.7–1.2))
	– None	4604 (79)	276 (79)	318 (80)		
	– Yes	1210 (21)	74 (21)	78 (20)		
	Maternal smoking during pregnancy (up to 32 weeks)				0.991 (1.0 (0.8–1.2))	0.681 (0.9 (0.7–1.2))
	– None	4620 (79)	275 (79)	318 (80)		
	– Yes	1194 (21)	75 (21)	78 (20)		
At birth						
	Breast feeding at any time point				0.387 (0.9 (0.7–1.1))	0.486 (0.9 (0.7–1.2))
	– No	991 (17)	64 (18)	74 (19)		
	– Yes	4823 (83)	286 (82)	322 (82)		
	Breast feeding duration across time points				0.859	0.474
	– Never	1254 (22)	74 (21)	92 (23)		
	– < 3 months	1373 (24)	76 (22)	93 (23)		
	– 3–5 months	997 (17)	59 (17)	68 (17)		
	– > 6 months	2190 (38)	142 (40)	144 (36)		
	Birthweight of child (g)				0.023 (MD 53 (7.6–99.2))#	0.009 (MD 81.2 (20.3–142.0))#
	– Mean (SE)	3415 (7.8)	3394 (35.0)	3332 (31.1)		
	Birthweight of child				0.015 (1.5 (1.1–2.1))#	0.030 (1.6 (1.1–2.4))#
	– > 2500g	5524 (95)	326 (93)	365 (92)		
	– ≤ 2500g	290 (5)	24 (7)	31 (8)		

(*Continued*)

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Table 4. (*Continued.*)

Data category	Parameter	No COM ($n = 5814$) (n (%))	Mild COM ($n = 350$) (n (%))	Significant COM ($n = 396$) (n (%))	No *vs* mild or significant *P*-value (OR or MD (95% CI))	No or mild *vs* significant *P*-value (OR or MD (95% CI))
	Gestational age of child (weeks)				0.040 (MD 0.2 (0.1–0.3))[#]	0.134 (MD 0.1 (0.1–1.2))
	– Mean (SE)	39.5 (0.03)	39.3 (0.2)	39.3 (0.1)		
	Gestational age of child				0.005 (1.6 (1.1–2.2))[#]	0.001 (1.8 (1.3–2.7))[#]
	– ≥ 37 weeks	5514 (95)	328 (94)	359 (91)		
	– < 37 weeks	300 (5)	22 (6)	37 (9)		
	Child has ever used a dummy/pacifier					
	– No	3080 (52)	186 (53)	207 (52)	0.936 (1.0 (0.9–1.2))	0.850 (1.0 (0.8–1.3))
	– Yes	2734 (47)	164 (47)	188 (48)		

All variables shown are derived from questionnaire data reported by the parent(s) when the child was 6, 18, 30, 42, 57, 69, 81, 91 and 103 months. If not significant, *p*-values only, resulting from the chi-square test, are reported for tables greater than 2 × 2. *A child was deemed to react to an allergen if the weal or flare was ≥ 2 mm at the age seven focus clinic. Children were excluded if they did not react to the positive allergen or did react to the negative control. These excluded children were imputed along with the missing data; [†]the child attended day care, as reported by the parent, at 15, 24 and 38 months; [‡]a measure of the number of persons in the household divided by the number of rooms available (including the kitchen if large enough to eat in); **child had some exposure to smoking (passive smoking) at any point up to 54 months; [§]mother reported smoking during pregnancy (at any time); [#]significant value. COM = chronic otitis media; OR = odds ratio; MD = mean difference; SE = standard error

Table 5. Multivariate model 1 (original plus imputed data, $n = 6560$)

Parameter	No COM* (n (%))	Mild or significant COM[†] (n (%))	No COM *vs* mild or significant COM (Adjusted *p*-value)	No COM *vs* mild or significant COM (Adjusted OR (95% CI))
Tympanometry (age 7)				
– Type A	4464 (77)	344 (46)		
– Type C1/C2	1037 (18)	220 (29)	<0.001[‡]	2.4 (1.9–2.9)[‡]
– Type B	313 (5)	183 (25)	<0.001[‡]	4.6 (3.5–5.9)[‡]
Pus or mucus leaking from the child's ear				
– Never	4439 (76)	404 (54)		
– At least once	1375 (24)	342 (46)	<0.001[‡]	1.4 (1.3–1.6)[‡]
Child had grommets inserted (by age 9)				
– No	5634 (97)	563 (75)		
– Yes	180 (3)	183 (25)	<0.001[‡]	5.0 (3.9–6.5)[‡]
Gestational age				
– ≥ 37 weeks	5514 (95)	687 (92)		
– < 37 weeks	300 (5)	59 (8)	0.040[‡]	1.4 (1.1–1.9)[‡]

*$n = 5814$; [†]$n = 746$; [‡]significant value. COM = chronic otitis media; OR = odds ratio; CI = confidence interval

to multiple insertions would suggest a dose–response relationship between severity of Eustachian tube dysfunction or OME and risk of chronic otitis media. The relationship between the physiology of the adenoids, Eustachian tube and the formation of chronic otitis media is likely to be complex and cannot be directly quantified in this study. Our findings, in combination with previous studies lend support to an interaction between the three.

Various models of chronic otitis media pathogenesis have been proposed.[34–42] One of the principle theories proposes chronic otitis media is related to poor middle-ear ventilation via Eustachian tube dysfunction. This theory suggests that chronic lack of middle-ear ventilation results in negative middle-ear pressures. In combination with multiple infections and weakening of the tympanic membrane, this results in progressive retraction of the ear drum.[40] Entrapment of keratin (produced by the surface of the tympanic membrane) within the pocket leads to formation of the cholesteatoma. Added infection though microbial colonisation and progressive erosion of middle-ear structures results in the typical clinical symptoms of hearing loss and otorrhoea.

This retraction theory of cholesteatoma is supported by evidence that cholesteatoma is often associated with Eustachian tube dysfunction.[43,44] In patients with chronic otitis media, a high proportion show chronic otitis media findings in the contralateral ear.[45,46] Chronic otitis media, in all of its forms, is particularly present in patients with cleft palate where Eustachian tube function is known to be disrupted.[22,23] Chronic otitis media is associated with particular variations in Eustachian tube anatomy and can be more prevalent in certain ethnic groups.[2]

Although this study demonstrates associations between ENT variables and the development of chronic otitis media by the age of nine, it is not appropriate to suggest a causal relationship. Some of the factors measured may be a result of chronic otitis media itself, including ear

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Table 6. Multivariate model 2 (original plus imputed data, $n = 6560$)

Parameter	No or mild COM* (*n* (%))	Significant COM† (*n* (%))	No or mild COM *vs* significant COM (Adjusted *p*-value)	No or mild COM *vs* significant COM (Adjusted OR (95% CI))
Tympanometry (age 7)				
– Type A	4464 (77)	344 (46)		
– Type C1/C2	1037 (18)	220 (29)	<0.001‡	2.5 (2.0–3.3)‡
– Type B	313 (5)	183 (25)	<0.001‡	5.4 (3.8–7.9)‡
Pus or mucus leaking from the child's ear				
– Never	4645 (75)	197 (50)		
– At least once	1519 (25)	199 (50)	<0.001‡	1.9 (1.5–2.3)‡
Child had grommets inserted (by age 9)				
– Yes	5909 (96)	288 (73)		
– No	255 (4)	108 (27)	<0.001‡	3.9 (2.9–5.1)‡
Gestational age				
–≥ 37 weeks	5842 (95)	359 (91)		
–< 37 weeks	322 (5)	37 (9)	0.014‡	1.6 (1.1–2.4)‡

*$n = 6164$; †$n = 396$; ‡significant value. COM = chronic otitis media; OR = odds ratio; CI = confidence interval

discharge, hearing loss and abnormal tympanometry or audiometry, and therefore should be considered as markers of risk of associated chronic otitis media. The association between chronic otitis media and some surgical interventions (including grommet insertion, adenoidectomy and tonsillectomy) may also reflect medical treatment of the condition itself.

A strong association was observed between preterm birth and presence of chronic otitis media. To our knowledge, this finding has not previously been reported in the literature although associations between preterm delivery, acute otitis media and OME have been identified.[47–49]

Although age of mother was associated with chronic otitis media when used as a continuous variable, the mean difference was very small, and it was not considered to be clinically significant. It is probable that the small differences are due to an increased sample size and therefore a high power, rather than any statistical difference. Age of the mother, as a categorical variable, was not an independent predictor of chronic otitis media (Table 2).

A number of factors, suggested by previous studies to be associated with the formation of chronic otitis media, were not supported by our results.[6,8–11,13,15–17] No association was found between chronic otitis media and sex of the child, parental social class, parental smoking, child care arrangements, crowding, number of siblings, maternal education level or a history of respiratory infections (Tables 2, 3 and 4). In 2015, Khalid-Raja *et al.* examined UK Hospital Episode Statistics data for cholesteatoma surgery and found a positive association with the deprivation index of the health authority.[50] No relationship between the presence of chronic otitis media at the age of nine and indicators of social deprivation were found here when using the social circumstances of the family rather than of the area.

The strengths of this study are that it is, to our knowledge, the largest prospective population study on this topic and therefore less prone to biases inherent in smaller retrospective studies. The video-otoscopic images of the tympanic membrane provide a measure of chronic otitis media that does not rely on parental report or surgical treatment. Limitations of the study include the fact that children attending the nine-year-old child review clinic (at which otoscopic images were taken) were more likely to be female, white, have a higher parental social class and higher education level of the mother. However, these factors were not associated with chronic otitis media in our analyses; consequently, the selection bias is unlikely to have influenced the nature of the associations measured.

- It is unclear why some children develop chronic otitis media
- A total of 6560 children underwent otoscopic photography at age nine as part of a prospective, longitudinal cohort study
- Five per cent of children were diagnosed with mild chronic otitis media and 6 per cent with more significant chronic otitis media
- The development of chronic otitis media by the age of nine was associated with a history of otorrhoea, snoring, grommet insertion, adenoidectomy, tonsillectomy, hearing loss, abnormal tympanograms and preterm birth
- Some associations suggested by previous published studies (sex of the child, socioeconomic group, parental smoking, maternal education, attendance at childcare, crowding and number of siblings) were not found to be significant predictors in this analysis
- This represents the largest prospective cohort study of factors associated with the development of paediatric chronic otitis media to date

Patterns of chronic otitis media differ with world geography and ethnicity.[2] As such, this study may only identify associations for the UK or similar populations. The strong association with multiple grommet insertions, type B or C tympanograms, and ear discharge of pus would seem to support the role of Eustachian tube dysfunction and prolonged OME as a risk factor for developing chronic otitis media.[40,43–46]

Conclusion

This is the largest prospective cohort study looking at the associations between the development of paediatric chronic otitis media (by the age of nine) and health and social factors. The key findings are strong associations between the presence of chronic otitis media at age nine and early reported history of otitis media, tympanometric evidence of middle-ear effusion and negative middle-ear pressure at age seven, hearing loss at

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age seven and a history of grommet treatment. Preterm birth and low birthweight were also predictive factors. An association was also found between the development of chronic otitis media and prolonged snoring, adenoidectomy or tonsillectomy.

Some associations suggested by previous published studies (sex of the child, socioeconomic group, parental smoking, maternal education, attendance at childcare, crowding, number of siblings) were not found to be significant predictors in this analysis.

It is not possible through our study method to show a causal relationship between chronic otitis media and the variables measured. A number of these variables may be related to symptoms or treatment of suspected chronic ear disease. The evidence presented in this study would support a role for prematurity, low birth weight, early acute ear disease, Eustachian tube pathology and upper airway resistance (snoring, adenoidectomy or tonsillectomy) in the pathogenesis of chronic otitis media.

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Competing interests. None declared

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