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Factors associated with the development of paediatric chronic otitis media by age 9 - A prospective longitudinal cohort study of 6560 children.

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Conflicts of interest

None to declare

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<u>Abstract</u>

Objective: To study social, health and environmental factors associated with the development of chronic otitis media (COM) by age 9.

Method: Prospective, longitudinal, birth cohort study of 6560 children, reviewed at age 9. COM defined as previous surgical history or video-otoscopic changes of tympanic membrane retraction, perforation or cholesteatoma. Non-affected children used control group.

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

Keywords: Otitis media; Cholesteatoma; Tympanic membrane perforation; Paediatrics; Risk factors; Cohort studies; Hearing loss; Otologic Surgical Procedures; Middle ear ventilation; Snoring; Tonsillectomy; Adenoidectomy

Introduction

Otitis media (OM) is a broad term used to describe an inflammatory process within the middle ear cleft. OM, in all its forms, represents a major worldwide health burden¹. Chronic otitis media (COM) is characterised by more long-term changes to the shape and function of the eardrum, including tympanic membrane (TM) retraction, perforation and cholesteatoma. COM is a leading cause of permanent hearing loss, especially within developing counties²⁻⁴. 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 COM increases the risk of serious and potentially life-threatening complication including mastoiditis, meningitis, intracranial venous sinus thrombosis and intracranial abscess formation⁵.

Whilst acute otitis media (AOM) and otitis media with effusion (OME) are common in childhood, COM is relatively rare¹. In the United Kingdom (UK), the prevalence, in British adults, of active and inactive middle ear disease is around 1.5% and 2.6% respectively⁶. It is unclear why some children with a propensity for AOM or OME progress to COM, whilst others do not. Numerous studies have attempted to identify risk factors for COM⁶⁻¹⁸. 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 COM in children^{9, 19}.

The Avon Longitudinal Study of Parents and Children (ALSPAC) 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 their tympanic membranes at age 9 years. A previous study has reviewed these images and reported the prevalence of COM changes including TM retraction, perforation and undiagnosed cholesteatoma²⁰. Retraction of the TM pars flaccida and pars tensa was seen in 9.6% and 7.9% of cases respectively. There were 15 cases of suspected cholesteatoma.

The aim of this study is to identify associations and potential risk factors for the development of paediatric COM at age 9. The prospective cohort design allows factors associated with chronic otitis media to be identified without recall bias.

Materials and Method

The Avon Longitudinal Study of Parents and Children (ALSPAC).

ALSPAC or "Children of the 90s study" recruited 14,541 pregnant mothers resident in a defined area (Avon in the southwest of the UK) and with 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 examination²¹. The ALSPAC 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 ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

<u>Study sample</u>

The study sample consisted of children within ALSPAC who attended a 9-year-old review "Focus clinic" with video-otoscopic data available. Children with a history of cleft lip and/or palate (CLP) were excluded. CLP is known to be a strong independent risk factor for the development of COM and further analysis of the associations/risk factors for these children was deemed unlikely to be informative ^{22, 23}.

<u>Outcome data</u>

Chronic Otitis Media

At the 9-year-old Focus clinic, data collected included video-otoscopic imaging of the child's TM and a parental interview regarding the child's Ear, Nose and Throat (ENT) surgical history. This study utilises the method of obtaining, coding and staging the TM images described in a previous paper²⁰. For the purposes of this study, COM was defined and categorised as:

- Significant COM: Video-otoscopic evidence of stage two retraction of the pars tensa or flacida, perforation, cholesteatoma/attic crust, or history of surgery for cholesteatoma or perforation.
- 2) Mild COM: Video-otoscopic evidence of stage one retraction of the pars tensa or flacida.
- No COM: Video-otoscopic evidence of normal tympanic membrane, with or without middle ear effusion, ventilation tube or tympanosclerosis.

Where an image of the TM was available for one ear only, the outcome of that child was categorised according to that ear only. This was deemed appropriate due to the fact that, of those children with data for both ears available, if no COM was recorded in one ear, 94% of those children also had no COM recorded in the other ear. This system of classification is consistent with previous classification systems used for COM²⁴.

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/mucus (not wax) leaking from ears, 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/mucus leakage; breath holding and snoring; early snoring, prolonged snoring; cough count, fever with a cough. All of these variables are defined in more detail in the relevant table legend.

At the 9-year-old Focus clinic, information was gathered about the child's history of ENT surgery including: ear surgery for COM; insertion of grommets (categorised as none, once or more than once); history of adenoidectomy; history of tonsillectomy.

Information about the child's hearing and middle ear function were available from the 7-yearold Focus clinic.

Child, maternal and socioeconomic factors

Mother's smoking in pregnancy 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 <37 weeks or ≥37 weeks) were obtained from the maternity records.

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; duration of breastfeeding. Information on dummy (also known as pacifier, soother or comforter) use was reported in maternal questionnaires when the child was age 4 weeks, 6 and 24 months. A variable of any dummy/pacifier use was derived. Mother's history of grommets was obtained by parental questionnaire.

Additional medical factors

Information on allergy was obtained using skin prick test responses carried out at the age 7 Focus clinic ²⁵. Atopic dermatitis was measured according to the ISAAC 1994 protocol at the 7-year-old Focus clinic²⁶⁻²⁸. 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. The crowding index was calculated (definition in table legend). 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 about the child's exposure to smoking and a variable was derived of any exposure to smoke.

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.

The Little's MCAR (missing completely at random) 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 Chi-square test and logistic regression. Continuous data were compared using 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 (OR) and adjusted OR resulting from logistic regression were reported alongside 95% CI (confidence interval). A fully adjusted model is also presented, where univariate predictors with a p value < 0.1 were included.

It is uncertain if "mild COM" changes (stage one retraction of the pars tensa or flaccida) represent temporary changes in the appearance of the TM, or reflect a milder form of COM. For this clinical based reason, two sets of sub group analyses were undertaken, comparing:

Model 1: No COM vs. mild or significant COM

Model 2: No or mild COM vs. significant COM

Results and Analysis

Full information on the number of ALSPAC participants can be found elsewhere^{21, 29}. 14,062 surviving children (at one year) were recruited to the study (Figure 1). Of these, 6,935 (49%) children attended the ALSPAC 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 analysis.

During the clinic visit, COM data (video-otoscopic imaging) could not be obtained for either ear for 330 (5%) children (reasons included child and/or parent declined, equipment availability and 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%) participants who had no evidence of COM. Of the remaining participants, 350 (5%) were categorised with mild COM and 396 (6%) with significant COM.

Of those with significant COM, 13 participants were categorised with significant COM due to a clinical history of repaired TM perforation; 9 due to a history of cholesteatoma. The remaining were characterised from 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 Tables A, and additional descriptive data are presented in supplementary Table B.

Table 2 presents the univariate comparisons which showed evidence of a significant association between children with and without COM (any associations that were tested and deemed not to show evidence of significance are presented in the supplementary material). Parental social class, sex of the child and maternal educational level were not associated with the presence of COM. Age of mother at birth was associated with the presence of COM (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 a significant univariate predictors of COM. 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 7 (Table 2).

For the majority of additional variables, there was no strong evidence of an association with COM (supplementary material), 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/pacifier were not associated with presence of COM (Table 2).

Multivariate models are presented in Table 3. For both models significant independent predictors included an early history of pus/mucus, a history of grommet insertion and a gestational age <37 weeks (Table 3). Type B or C tympanometric recordings at age 7 were also an independent predictor of COM (Table 3).

The fully adjusted model for no COM vs. mild COM/significant COM (all factors with a univariate p value < 0.01) is presented in supplementary table C. It can be seen that the models, and OR's 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 COM in children by the age of nine.

A comparison of results from the two-analysis models demonstrates that the group with "mild COM" have a profile more similar to the "No COM" group. The fact that children with mild COM share more traits with the "no COM" group, suggests that mild retraction of the tympanic membrane may be transient change and that progression to more significant COM is not inevitable. This may have implications for the clinical assessment and management of early TM retraction in the paediatric population and would support a conservative management approach unless more significant signs and symptoms of COM become apparent.

Factors that were univariately associated with the development of COM by the age of 9 included a history of ear discharge, prolonged snoring, grommet insertion (especially multiple insertions), adenoidectomy and/or tonsillectomy, abnormal tympanometry (especially type B), hearing loss at age 7, low birthweight and gestational age under 37 weeks. Multivariate analysis of these factors reveals a more refined picture. Multiple variables show a high degree of multicollinearity (both clinically and statistically). ENT factors of a history of pus/mucus from the ears, previous grommet insertion and type B or C tympanometry remained independent predictors of COM 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 COM, this significance is lost in the multivariate analysis. This appears to be due to the fact that it is highly related to a number of other variables (pus/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 apnoea³⁰⁻ ³². A link between COM and adenoidectomy has been proposed by previous studies. A 2010 retrospective cohort study that suggested adenoidectomy may have a protective role in reducing the risk of developing paediatric COM¹⁴. Our findings suggest that the adenoidectomy, tonsillectomy and nocturnal airway obstruction may have roles to play as risk factors for the development of COM, although the pathophysiology underpinning this 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 COM during multivariate analysis. UK studies have shown that adenoidectomy at the time of grommet insertion reduces the risk of recurrent OME³³.

The association between COM and abnormal tympanometry supports the concepts that middle ear pressure homeostasis and ET function may be important in the formation of COM. The lower odds ratio found in patients with type C1/2 compared to type B tympanograms, and only a single grommet insertion compared to multiple insertions would suggest a dose response relationship between severity of ET dysfunction/OME and risk of COM. The relationship between the physiology of the adenoids, ET and the formation of COM 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 COM pathogenesis have been proposed³⁴⁻⁴². One of the principle theories proposes COM is related to poor middle ear ventilation via Eustachian tube (ET) 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 drum⁴⁰. Entrapment of keratin (produced by the surface of the TM) 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 otorrhea.

This retraction theory of cholesteatoma is supported by evidence that cholesteatoma is often associated with ET dysfunction^{43, 44}. In patients with COM, a high proportion show COM findings in the contralateral ear^{45, 46}. COM, in all of its forms, is particularly present in patients with cleft palate where ET function is known to be disrupted^{22, 23}. COM is associated with particular variations in ET anatomy and can be more prevalent in certain ethnic groups².

Whilst this study demonstrates associations between ENT variables and the development of COM by the age of nine, it is not appropriate to suggest a causal relationship. Some of the factors measured may be a result of COM itself, including ear discharge, hearing loss and abnormal tympanometry or audiometry, and as such should be considered as markers of risk of associated COM. The association between COM 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 COM; to our knowledge this finding has not previously been reported in the literature although associations between preterm delivery, AOM and OME have been identified⁴⁷⁻⁴⁹.

Although age of mother was associated with COM 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 COM (Table 2a).

A number of factors, suggested by previous studies to be associated with the formation of COM, were not supported by our results^{6, 8-11, 13, 15-17}. No association was found between COM 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 (see supplementary material). 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 authority⁵⁰. No relationship between the presence of COM at the age of 9 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 as such less prone to biases inherent in smaller retrospective studies. The video-otoscopic images of the TM provide a measure of COM that does not rely on parental report or surgical treatment. Limitations of the study include the fact that children attending the 9 year 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 COM in our analyses; consequently the selection bias is unlikely to have influenced the nature of the associations measured.

Patterns of COM differ with world geography and ethnicity². As such, this study may only identify associations for UK or similar populations. The strong association with multiple grommet insertions, type B/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 $COM^{40, 43-46}$.

Conclusion

This is the largest prospective cohort study looking at the associations between the development of paediatric COM (by the age of 9) and health and social factors. The key findings are strong associations between the presence of COM at age 9 and early reported history of otitis media, tympanometric evidence of middle ear effusion and negative middle ear pressure at age 7, hearing loss at age 7 and a history of grommet treatment. Preterm birth and low birthweight were also predictive factors. An association was also found between the development of COM and prolonged snoring, adenoidectomy and/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 this study method to show a causal relationship between COM 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, tonsillectomy) in the pathogenesis of COM.

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The authors have no competing interests to declare.

Summary

• It is unclear why some children develop chronic otitis media (COM).

- 6560 children underwent otoscopic photography at the age 9 as part of a prospective, longitudinal cohort study.
- 5% of children were diagnosed with mild COM and 6% with more significant COM
- The development of COM by the age of 9 was associated with a history of otorrhea, 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, 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.

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Legends for Figures and Tables

Figure 1. Study flow chart

Table 1. Demographics data of the study sample (n=6560)

Table 2a. Univariate comparisons of demographics data with the outcome variable (original plus imputed data n=6560)

Table 2b. Univariate comparison of ENT questionnaire data with the outcome variable (original plus imputed data n= 6560)

Table 2c. Comparison of additional variables with the outcome variables (original plus imputed data n=6560)

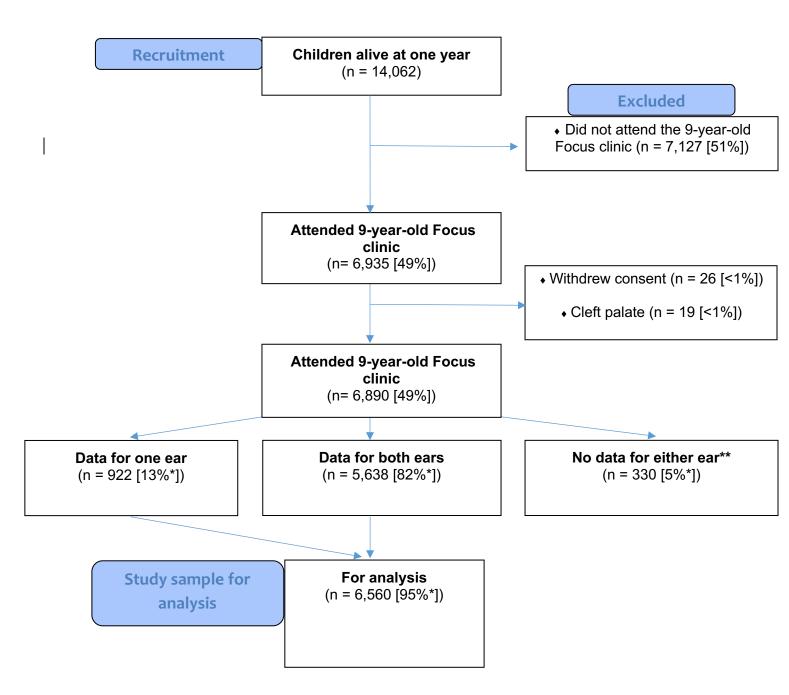
Table 3. Multivariate models (original plus imputed data n=6560)

Supplementary Table A. ENT derived data(n=6560)

Supplementary Table B. Additional variables (n=6560)

Supplementary Table C. Fully adjusted model (original plus imputed data n= 6560).

Figure 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), Ethic background (p = 0.655), social class (p = 0.942) and mother's highest education level (p = 0.759).

Table 1. Demographics data of the study sample (n=6560)

| | | Original data n (%)* | Original plus imputed data n (%)* |
|--|-------------------------|----------------------|-----------------------------------|
| Sex of child | Male | 3251 (50) | 3251 (50) |
| | Female | 3309 (50) | 3309 (50) |
| | Missing | 0 | |
| Child ethnic background | White | 5655 (96) | 6281 (96) |
| | Non-white | 230 (4) | 279 (4) |
| | Missing | 675 | |
| Parental social class ¹ | I (professional) | 897 (16) | 958 (15) |
| (Social class of the most advantaged parent) | 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 | |
| Mothers highest education qualification | CSE (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 | |

*unless otherwise stated ^ Education finished <16 years. ^^ Education up to 16 years. ^^^ Education at ≥18 years SD - Standard deviation

SE – Standard error

¹ The parents' social class was based on the Standard Occupational Classification (1990) of the mother or partner (whichever was the more advantaged) occupation at 32 weeks of pregnancy29. This was measured using the parents' occupation and based on a scale of I (professional), through II, III (divided into manual and non-manual), IV (partly-skilled occupations) and V (unskilled occupations).

| | | | n (%)* | | P val | P value (*) | |
|-----------------------------------|---------------------------|-------------|-------------|-----------------|-----------------------------|-----------------------------|--|
| | | No COM | Mild COM | Significant COM | No vs. mild / significant | No / mild vs. significant | |
| | | (n=5814) | (n=350) | (n=396) | | | |
| Sex of child | Male | 2894 (50) | 171 (49) | 186 (47) | 0.323 (OR 1.1 [0.9-1.3]) | 0.288 (OR 1.1 [0.9-1.4]) | |
| | Female | 2920 (50) | 179 (51) | 210 (53) | | | |
| Child ethnic background | White | 5563 (96) | 335 (96) | 383 (97) | 0.535 (OR 0.8 [0.5-1.5]) | 0.409 (OR 0.7 [0.4-1.5]) | |
| | Non-white | 251 (4) | 15 (4) | 13 (3) | | | |
| Parental social class | l (professional) | 856 (15) | 48 (14) | 54 (14) | 0.357 | 0.692 | |
| (highest parental class | II | 2529 (43) | 148 (42) | 184 (46) | | | |
| of the most advantaged | III (non-manual) | 1440 (25) | 82 (23) | 76 (19) | | | |
| parent) | 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) | | | |
| Mothers highest | CSE/Vocational (low)^ | 1235 (22) | 79 (14) | 86 (13) | 0.440 | 0.264 | |
| education qualification | O level (medium)^^ | 2105 (36) | 125 (36) | 128 (32) | | | |
| | A level/ Degree (high)^^^ | 2474 (27) | 146 (25) | 182 (31) | | | |
| Age of mother at birth (years) | Mean (SE) | 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 | ≤ 25 years | 915 (16) | 57 (16) | 59 (15) | 0.194 | 0.071 | |
| | 25 – 34 years | 4190 (72) | 252 (72) | 303 (77) | | | |
| | ≥ 35 years | 709 (12) | 41 (12) | 34 (9) | | | |

Table 2a. Univariate comparisons of demographics data with the outcome variable (original plus imputed data n= 6560)

*OR (odds ratio) with 95% CI (confidence intervals) or MD (mean difference) with 95% CI presented, as appropriate. If not significant, P values only, resulting

from the Chi-squared test, are reported for tables greater than 2x2.

COM = chronic otitis media

Significant result

^ Education finished <16 years. ^^ Education up to 16 years. ^^^ Education at ≥18 years

| Table 2b. Univariate comparison of ENT | questionnaire data with the outcome variable | (original plus imputed data n= 6560) |
|--|--|--------------------------------------|
| | | |

| | | n (%)* | | | P value (OR [95% CI])* | |
|--|------------------------------------|-----------|----------|-----------------|---------------------------|---------------------------|
| | | No COM | Mild COM | Significant COM | No vs. mild / significant | No / mild vs. significant |
| Reported** | | (n=5814) | (n=350) | (n=396) | | |
| Pus/mucus leaking from | Never ^R | 4439 (76) | 207 (59) | 197 (50) | | |
| the child's ear | 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 breathe for several seconds while | 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 ¹ | 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 | No | 5277 (91) | 302 (86) | 323 (82) | | |
| snorting) ² | 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) ¹ | 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]) |
| inserted (by age 9) | Did not have grommets ^R | 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 ³ | < 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 ^R | 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]) |
| | Туре В | 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 (better hearing ear), dB | < 20 dB | 5694 (98) | 333 (95) | 363 (92) | | |
| | ≥ 20 dB | 120 (2) | 17 (5) | 33 (8) | < 0.001 (3.4 [2.3-5.1]) | < 0.001 (4.0 [2.6-6.2]) |

* OR (odds ratio) with 95% CI (confidence intervals) presented as appropriate. If not significant, P values only, resulting from the Chi-squared test, are

reported for tables greater than 2x2.

** 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.

¹ Yes = a report of yes for at least one minute at least one 'yes often' / 'most nights' across all time points.

² Yes = a report of snoring for at least one minute at least two reports of 'most nights' across time points.

³ Cough count = % of times a cough was reported across all time points.

^R Reference category

Significant result

COM= chronic otitis media

Table 2c. Comparison of additional variables with the outcome variables (original plus imputed data n= 6560)

| | | n (%)* | | P value (OR* [95% CI]) | | |
|--|------|-----------|----------|------------------------|-----------------------|---------------------------|
| | | No COM | Mild COM | Significant COM | No vs. mild / | No / mild vs. significant |
| Reported** | | (n=5814) | (n=350) | (n=396) | significant | |
| Medical factors | | | | | | |
| Allergy ¹ (7 years) | No | 4575 (79) | 282 (81) | 319 (81) | | |
| | Yes | 1239 (21) | 68 (19) | 77 (19) | 0.264 (0.9 [0.7-1.1]) | 0.384 (0.9 [0.7-1.2]) |
| Atopic dermatitis (7 years) | No | 5347 (92) | 320 (91) | 366 (92) | | |
| | Yes | 467 (8) | 30 (9) | 30 (8) | 0.981 (1.0 [0.7-1.3]) | 0.786 (0.9 [0.6-1.4]) |
| Doctor diagnosis of asthma (91 months) | No | 4617 (79) | 278 (79) | 310 (78) | | |
| (nonuis) | Yes | 1197 (21) | 72 (21) | 86 (22) | 0.703 (1.0 [0.9-1.3]) | 0.594 (1.1 [0.8-1.4]) |
| Day care | | | | | | |
| Day care at any time (up to 38 months) ² | None | 3498 (60) | 203 (58) | 235 (59) | | |
| , | Yes | 2316 (40) | 147 (42) | 160 (41) | 0.525 (1.1 [0.9-1.3]) | 0.853 (1.0 [0.8-1.3]) |
| Day care regularly (38 months) ³ | No | 3862 (66) | 222 (63) | 261 (66) | | |
| | Yes | 1952 (34) | 128 (37) | 135 (34) | 0.317 (1.1 [0.9-1.3]) | 0.685 (1.1 [0.8-1.3]) |
| Day care 10+ hours per week (38 months) | No | 1051 (18) | 67 (19) | 64 (16) | | |
| | Yes | 4763 (82) | 283 (81) | 332 (84) | 0.671 (1.0 [0.8-1.3) | 0.362 (1.2 [0.8-1.7]) |
| Crowding | | | | | | |
| Number of other children in house (6 months) | 0 | 2613 (45) | 133 (38) | 180 (45) | | |
| monuts) | 1 | 2153 (37) | 153 (44) | 148 (37) | 0.261 | 0.848 |
| | >2 | 1047 (18) | 65 (19) | 68 (17) | | |
| Number of other children in house (81 months) | 0 | 606 (10) | 31 (9) | 36 (9) | | |
| | 1 | 3137 (54) | 185 (53) | 225 (57) | 0.430 | 0.413 |
| | >2 | 2071 (36) | 134 (38) | 136 (34) | | |

| Crowding index (8 months) ⁴ | ≤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) | 0.264 | 0.720 |
| | >1 | 788 (15) | 52 (17) | 58 (17) | | |
| Crowding index (33 months) ⁴ | ≤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) | 0.747 | 0.724 |
| | >1 | 396 (7) | 23 (7) | 29 (7) | | |
| Crowding index (81 months) ⁴ | ≤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) | 0.720 | 0.382 |
| | >1 | 781 (19) | 48 (18) | 60 (20) | | |
| Presence of mould in the home (8 | None ^R | 4069 (70) | 228 (65) | 267 (67) | | |
| months) | Not serious | 1274 (22) | 93 (27) | 90 (23) | 0.101 | 0.366 |
| | Serious | 471 (8) | 29 (8) | 39 (10) | | |
| Presence of damp in the home (8 months) | None ^R | 2836 (49) | 168 (48) | 192 (48) | | |
| montais) | Not serious | 2585 (44) | 157 (45) | 175 (44) | 0.818 | 0.851 |
| | Serious | 393 (7) | 24 (7) | 29 (7) | | |
| Smoking | | | | | | |
| Child exposure to smoke (up to 54 | None | 3237 (56) | 191 (54) | 212 (54) | | |
| months) ⁵ | Yes | 2577 (44) | 159 (45) | 184 (46) | 0.424 (1.1 [0.9-1.3]) | 0.430 (1.1 [0.9-1.3]) |
| Child exposure to smoke (6 months) | None | 3843 (66) | 233 (67) | 255 (64) | | |
| | Yes | 1971 (34) | 117 (33) | 141 (36) | 0.756 (1.0 [0.9-1.2]) | 0.526 (1.1 [0.9-1.4]) |
| Child exposure to smoke (38 months) | None | 3740 (64) | 215 (61) | 254 (64) | | |
| | Yes | 2074 (36) | 135 (39) | 142 (36) | 0.484 (1.1 [0.9-1.3]) | 0.971 (1.0 [0.8-1.3]) |
| Child exposure to smoke (54 months) | None | 3836 (66) | 221 (63) | 250 (63) | | |
| | Yes | 1978 (34) | 129 (37) | 146 (37) | 0.126 (1.1 [1.0-1.3]) | 0.300 (1.1 [0.9-1.4]) |

| Maternal smoking during pregnancy (at any time) ⁶ | None | 4700 (77) | 284 (78) | 326 (78) | | |
|--|------------|-------------|-------------|-------------|-----------------------|------------------------|
| | Yes | 1114 (23) | 66 (22) | 70 (22) | 0.584 (0.9 [0.8-1.2]) | 0.526 (0.9 [0.7-1.2]) |
| Material smoking during pregnancy | None | 4604 (79) | 276 (79) | 318 (80) | | |
| (up to18 weeks) | Yes | 1210 (21) | 74 (21) | 78 (20) | 0.775 (1.0 [0.8-1.2]) | 0.580 (0.9 [0.7-1.2]) |
| Maternal smoking during pregnancy (up to 32 weeks) | None | 4620 (79) | 275 (79) | 318 (80) | | |
| (up to 32 weeks) | Yes | 1194 (21) | 75 (21) | 78 (20) | 0.991 (1.0 [0.8-1.2]) | 0.681 (0.9 [0.7-1.2]) |
| At birth | | | | | | |
| Breast feeding at any time point^ | No | 991 (17) | 64 (18) | 74 (19) | | |
| | Yes | 4823 (83) | 286 (82) | 322 (82) | 0.387 (0.9 [0.7-1.1]) | 0.486 (0.9 [0.7-1.2]) |
| Breast feeding duration across time points^ | Never | 1254 (22) | 74 (21) | 92 (23) | | |
| points | < 3 months | 1373 (24) | 76 (22) | 93 (23) | 0.050 | 0.474 |
| | 3-5 months | 997 (17) | 59 (17) | 68 (17) | 0.859 | 0.474 |
| | > 6 months | 2190 (38) | 142 (40) | 144 (36) | | |
| Birthweight of child (g) | | 0445 (7.0) | 0004 (05.0) | 0000 (04 4) | 0.023 | 0.009 |
| | Mean (SE) | 3415 (7.8) | 3394 (35.0) | 3332 (31.1) | (MD 53 [7.6-99.2]) | (MD 81.2 [20.3-142.0]) |
| Birthweight of child | > 2500g | 5524 (95) | 326 (93) | 365 (92) | 0.015 | 0.030 |
| | ≤ 2500g | 290 (5) | 24 (7) | 31 (8) | (1.5 [1.1-2.1]) | (1.6 [1.1-2.4]) |
| Gestational age of child (weeks) | | | | | 0.040 | 0.134 |
| | Mean (SE) | 39.5 (0.03) | 39.3 (0.2) | 39.3 (0.1) | (MD 0.2 [0.1-0.3]) | (MD 0.1 [0.1-1.2]) |
| Gestational age of child | ≥ 37 weeks | 5514 (95) | 328 (94) | 359 (91) | 0.005 | 0.001 |
| | < 37 weeks | 300 (5) | 22 (6) | 37 (9) | (1.6 [1.1-2.2]) | (1.8 [1.3-2.7]) |
| Child ever use a dummy/ pacifier | No | 3080 (52) | 186 (53) | 207 (52) | | · · · |
| | Yes | 2734 (47) | 164 (47) | 188 (48) | 0.936 (1.0 [0.9-1.2]) | 0.850 (1.0 [0.8-1.3]) |

* Unless otherwise stated. MD – Mean difference. If not significant, P values only, resulting from the Chi-squared test, are reported for tables greater than

2x2.

** All variables 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.

¹A child was deemed to react to an allergen if the weal and/or flare was ≥2mm at the age 7 Focus clinic. Children were excluded if they didn't react to the positive allergen, or did react to the negative control. These excluded children were imputed along with the missing data.

² The child attended day care, as reported by the parent, at 15, 24 and 38 months.

³ 'Regular' was defined as general habit and not a one off.

⁴ 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).

⁵ Child had some exposure to smoking (passive smoking) at any point up to 54 months

⁶ Mother reported smoking during pregnancy (at any time).

^ Owing to a difference in time points, numbers may differ.

Table 3. Multivariate models (original plus imputed data n= 6560)

| | | | n (%) | No COM vs. mild / significant COM | | |
|---|---------------------|-----------------------|----------------------|-----------------------------------|----------------------|--|
| | | No COM | Mild/significant COM | Adjusted <i>p</i> value | Adjusted OR (95% CI) | |
| Model 1 | | (n=5814) | (n=746) | | | |
| Tympanometry (age 7) | Type A ^R | 4464 (77) | 344 (46) | | | |
| | Type C1 / C2 | 1037 (18) | 220 (29) | < 0.001 | 2.4 (1.9-2.9) | |
| | Туре В | 313 (5) | 183 (25) | < 0.001 | 4.6 (3.5-5.9) | |
| Pus/mucus leaking from the child's ear | e Never | 4439 (76) | 404 (54) | | | |
| | At least once | 1375 (24) | 342 (46) | < 0.001 | 1.4 (1.3-1.6) | |
| Child had grommets inserte by age 9) | ed 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) | |
| Model 2 | | | n (%) | No / mild COM vs. significant COM | | |
| Model 2 | | No/mild COM | Significant COM | | | |
| | | | - | Adjusted <i>p</i> value | Adjusted OR (95% CI) | |
| Tympanometry (age 7) | Type A ^R | (n=6164) 4464 (77) | (n=396) 344 (46) | | | |
| | Type C1 / C2 | 1037 (18) | 220 (29) | < 0.001 | 2.5 (2.0-3.3) | |
| | Туре В | 313 (5) | 183 (25) | < 0.001 | 5.4 (3.8-7.9) | |
| Pus/mucus leaking from the child's ear | | 4645 (75) | 197 (50) | | | |
| | At least once | 1519 (25) | 199 (50) | < 0.001 | 1.9 (1.5-2.3) | |
| Child had grommets inserte by age 9) | ed No | 5909 (96) | 288 (73) | | | |
| | Yes | 255 (4) | 108 (27) | < 0.001 | 3.9 (2.9-5.1) | |
| Sestational age | ≥ 37 weeks | 5842 (95) | 359 (91) | | | |
| | < 37 weeks | 322 (5) | 37 (9) | 0.014 | 1.6 (1.1-2.4) | |

^R Reference category COM = chronic otitis media. OR = odds ratio. CI = confidence interval.

Supplementary table A. ENT derived data(n=6560)

| Reported** | | Original data n (%)* | Original plus imputed data n (%)* | | |
|-------------------------------------|------------------------|----------------------|-----------------------------------|--|--|
| Pus/mucus leaking from the | Never | 4690 (74) | 4842 (74) | | |
| child's ear | Once | 998 (16) | 1018 (16) | | |
| | >1 | 673 (11) | 700 (11) | | |
| | Missing | 199 | | | |
| Child holds breathe for several | No | 4140 (70) | 4583 (70) | | |
| seconds while sleeping ¹ | Yes | 1805 (30) | 1977 (30) | | |
| | Missing | 615 | | | |
| Child ever snores ¹ | No | 5274 (83) | 5449 (83) | | |
| | Yes | 1051 (17) | 1111 (17) | | |
| | Missing | 235 | | | |
| Child snores on at least two | No | 5807 (92) | 5903 (90) | | |
| time points (prolonged snoring) | Yes | 518 (8) | 657 (10) | | |
| | Missing | 235 | | | |
| Child snores at 6 and 18 | No | 5642 (96) | 6023 (92) | | |
| months (early snoring) ³ | Yes | 261 (4) | 537 (6) | | |
| | Missing | 657 | | | |
| Mother reported a history of | No | 5133 (98) | 6424 (98) | | |
| naving grommets inserted | Yes | 85 (2) | 136 (2) | | |
| | Missing | 1342 | | | |
| Child had grommets inserted | Did not have grommets | 6166 (95) | 6197 (94) | | |
| (by age 9) | Grommets inserted once | 291 (5) | 293 (4) | | |
| | Grommets inserted >1 | 66 (1) | 70 (1) | | |
| | Missing | 37 | | | |
| Child had tonsils removed (by | No | 6414 (98) | 6445 (98) | | |
| age 9) | Yes | 112 (2) | 115 (2) | | |

| | Missing | 34 | |
|------------------------------|---------------------------|------------|-------------|
| Child had adenoids removed | No | 6322 (97) | 6352 (97) |
| by age 9) | Yes | 204 (3) | 208 (3) |
| | Missing | 34 | |
| Cough count ⁴ | Mean | 61 (SD 28) | 60 (SE 0.4) |
| ever reported alongside a | No cough reported / never | 1515 (25) | 1664 (25) |
| cough⁵ | Fever with some attacks | 3462 (57) | 3681 (56) |
| | Fever with every attack | 1155 (19) | 1215 (19) |
| | Missing | 428 | |
| ympanometry at age 7 (better | Туре А | 4059 (75) | 4808 (73) |
| unctioning ear) ⁶ | Type C1 | 646 (12) | 790 (12) |
| | Type C2 | 360 (7) | 466 (7) |
| | Туре В | 369 (7) | 496 (8) |
| | Missing | 1126 | |
| Audiometry age 7 (better | < 20 dB | 5100 (98) | 6390 (97) |
| nearing ear) ⁷ | ≥ 20 dB | 126 (2) | 170 (3) |
| | Missing | 1334 | |

*Unless otherwise stated.

** 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.

¹ Yes = a report of yes for at least one minute, with at least one 'yes often' or 'most nights' across all time points.

² Yes = a report of snoring for at least one minute, with at least two reports of 'most nights' across time points.

³ Categorised as positive if there was a report of snoring 'most nights' at either 6 or 18 months

⁴ Cough count = % of times a cough was reported across all time points (cough count was considered missing if > 50% of time points were missing).

⁵ Categorised as 'no cough reported or no fever recorded with any cough attack', 'fever with some cough attacks' or 'fever with every cough attack'.

⁶ Tympanograms were coded according to Fieullau-Nikolajsen's modification of Jerger's classification, categorised as type A, C1/C2 or B in the better functioning ear²⁸.

⁷ Hearing thresholds were measured using pure tone audiometry across 0.5, 1, 2 and 4 kHz in the left and right ears. The air conduction average hearing threshold in the better hearing ear was calculated.

SD - Standard deviation, SE - Standard error

Supplementary Table B. Additional variables (n=6560)

| Reported** | | Original data n (%)* | Original plus imputed data n (%)* |
|---|----------|----------------------|-----------------------------------|
| Medical factors | | | |
| Allergy (7 years) ¹ | No | 3875 (79) | 5176 (79) |
| | Yes | 1032 (21) | 1384 (21) |
| | Excluded | 111 | |
| | Missing | 1542 | |
| Atopic dermatitis (7 years) ² | No | 5268 (92) | 6032 (92) |
| | Yes | 464 (8) | 528 (8) |
| | Missing | 828 | |
| Doctor diagnosis of asthma (91 months) | No | 4153 (80) | 5205 (79) |
| | Yes | 1050 (20) | 1355 (21) |
| | Missing | 1357 | |
| Day care | | | |
| Day care at any time (up to 38 months) ³ | None | 3021 (57) | 3936 (60) |
| | Yes | 2303 (43) | 2624 (40) |
| | Missing | 1236 | |
| Day care regularly (38 months) ⁴ | No | 3490 (62) | 4100 (63) |
| | Yes | 2112 (38) | 2460 (38) |
| | Missing | 958 | |
| Day care 10+ hours per week (38 months) | No | 4665 (83) | 5378 (82) |
| | Yes | 937 (17) | 1182 (18) |
| | Missing | 958 | |
| Crowding | | | |
| Number of children in house (6 months) | 0 | 2595 (45) | 2926 (44) |
| | 1 | 2177 (38) | 2454 (37) |
| | >2 | 1035 (18) | 1180 (18) |
| | Missing | 753 | |

| Number of children in house (81 months) | 0 | 546 (10) | 673 (10) |
|--|-----------------------|-----------|-----------|
| | 1 | 2888 (55) | 3547 (54) |
| | >2 | 1865 (35) | 2340 (36) |
| | Missing | 1261 | |
| Crowding index (8 months)⁵ | ≤0.5 | 837 (16) | 1022 (16) |
| | 0.5-0.75 | 2192 (41) | 2479 (38) |
| | 0.75-1 | 1811 (34) | 2161 (33) |
| | >1 | 558 (10) | 898 (13) |
| | Missing | 1162 | |
| Crowding index (33 months)⁵ | ≤0.5 | 1042 (20) | 1269 (20) |
| | 0.5-0.75 | 2042 (40) | 2474 (38) |
| | 0.75-1 | 1777 (34) | 2370 (36) |
| | >1 | 315 (6) | 447 (7) |
| | Missing | 1384 | |
| Crowding index (81 months) ⁵ | ≤0.5 | 712 (14) | 887 (14) |
| | 0.5-0.75 | 1838 (36) | 2206 (34) |
| | 0.75-1 | 2123 (41) | 2578 (39) |
| | >1 | 501 (10) | 889 (13) |
| | Missing | 1386 | |
| Presence of mould in the home (8 months) | None | 4097 (75) | 4912 (75) |
| | Not serious | 1236 (23) | 1465 (22) |
| | Fairly / Very serious | 143 (3) | 183 (3) |
| | Missing | 1084 | |
| Presence of damp in the home (8 months) | None | 2850 (52) | 3196 (49) |
| | Not serious | 2356 (43) | 2917 (45) |
| | Fairly / Very serious | 289 (5) | 447 (6) |
| | Missing | 1065 | |
| Smoking | | | |

| Child any exposure to smoke (up to 54 months) ⁶ | None | 2654 (51) | 3260 (50) |
|--|------------|-----------|-----------|
| - · · · · / | Yes | 2552 (49) | 3300 (50) |
| | Missing | 1354 | |
| Child exposure to smoke (6 months) | None | 3845 (67) | 4331 (66) |
| | Yes | 1876 (33) | 2229 (34) |
| | Missing | 839 | |
| Child exposure to smoke (38 months) | None | 3505 (63) | 4209 (62) |
| | Yes | 2033 (37) | 2351 (38) |
| | Missing | 1022 | |
| Child exposure to smoke (54 months) | None | 3575 (65) | 4306 (66) |
| | Yes | 1912 (35) | 2254 (34) |
| | Missing | 1073 | |
| Maternal smoking during pregnancy (at any time) ⁷ | None | 4730 (82) | 5310 (81) |
| | Yes | 1076 (19) | 1250 (19) |
| | Missing | 754 | |
| Maternal smoking during pregnancy (18 weeks) | None | 4747 (83) | 5374 (82) |
| | Yes | 989 (17) | 1186 (18) |
| | Missing | 824 | |
| Maternal smoking during pregnancy (32 weeks) | None | 4829 (87) | 5631 (85) |
| | Yes | 744 (13) | 929 (14) |
| | Missing | 987 | |
| At birth | | | |
| Breast feeding at any time point^ | No | 977 (16) | 1129 (17) |
| | Yes | 5019 (84) | 5431 (83) |
| | Missing | 564 | |
| Breast feeding duration across time points [^] | Never | 1164 (20) | 1419 (22) |
| | <3 months | 1327 (23) | 1542 (24) |
| | 3-5 months | 977 (17) | 1123 (17) |
| | 6 months + | 2228 (39) | 2476 (38) |
| | Missing | 864 | |

| Birthweight of child | > 2500g | 5832 (95) | 6215 (95) |
|----------------------------------|------------|-----------|-----------|
| | ≤ 2500g | 311 (5) | 345 (5) |
| | Missing | 417 | |
| Gestational age of child | < 37 weeks | 339 (6) | 359 (5) |
| | ≥ 37 weeks | 5872 (95) | 6201 (95) |
| | Missing | 349 | |
| Child ever use a dummy/ pacifier | No | 3160 (54) | 3474 (53) |
| | Yes | 2683 (46) | 3086 (47) |
| | Missing | 717 | |

* Unless otherwise stated

** All variables 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.

¹A child was deemed to react to an allergen if the weal and/or flare was \geq 2mm at the age 7 Focus clinic. Children were excluded if they didn't react to the positive allergen, or did react to the negative control. For this study children were categorised with an allergy if they were positive for house dust mite, mixed grasses or cat. These excluded children were imputed along with the missing data.

² Categorised as present if >1 cm in diameter in any of the following areas: around the eyes, the sides or front of the neck, in front of the elbows, behind the knees or in front of the ankles

³ The child attended day care, as reported by the parent, at 15, 24 and 38 months.

⁴ 'Regular' was defined as general habit and not a one off.

⁵ 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). The crowding index was derived from the number of persons in the household divided by the number of rooms available in the house (<0.5, 0.5-<0.75, 0.75-<1 or

 \geq 1), where the higher the number the greater the crowding.

⁶ Child had some exposure to smoking (passive smoking) at any point up to 54 months.

⁷ Mother reported smoking during pregnancy (at any time).

^ Owing to a difference in time points, numbers may differ.

| | | n (%) | | Adjusted <i>p</i> value | Adjusted OR (95% CI) | |
|--|---------------------|--|----------|-------------------------|-----------------------------------|--|
| Model 1 | | No COM (n=5814) Mild / significant COM (n=746) | | No COM vs. m | No COM vs. mild / significant COM | |
| child's ear | Never | 4439 (76) | 404 (54) | | | |
| | At least once | 1375 (24) | 342 (46) | < 0.001 | 1.4 (1.3-1.6) | |
| Child snores on at least two time points (prolonged snoring)* | No | 5277 (91) | 625 (84) | | | |
| | Yes | 537 (9) | 121 (16) | 0.242 | 1.2 (0.9-1.5) | |
| (by age 9) | No | 5634 (97) | 563 (75) | | | |
| | Yes | 180 (3) | 183 (25) | < 0.001 | 4.9 (3.6-6.7) | |
| Child reported having tonsils removed (age 9) | No | 5738 (99) | 707 (95) | | | |
| | Yes | 76 (1) | 39 (5) | 0.286 | 0.7 (0.4-1.3) | |
| Child reported having adenoids removed (age 9) | No | 5692 (98) | 660 (88) | | | |
| | Yes | 122 (2) | 86 (12) | 0.418 | 1.2 (0.8-1.9) | |
| Tympanometry at age 7 (better functioning ear) | Type A ^R | 4464 (77) | 344 (46) | | | |
| | Type C1 / C2 | 1037 (18) | 220 (29) | < 0.001 | 2.3 (1.9-2.9) | |
| | Туре В | 313 (5) | 183 (25) | < 0.001 | 4.5 (3.3-6.1) | |
| Audiometry age 7 (better hearing ear) | < 20 dB | 5694 (98) | 696 (93) | | | |
| | ≥ 20 dB | 120 (2) | 50 (7) | 0.996 | 1.0 (0.6-1.8) | |
| | > 2500g | 5524 (95) | 691 (93) | | | |
| | ≤ 2500g | 290 (5) | 55 (7) | 0.463 | 1.2 (0.8-1.4) | |
| Gestational age | ≥ 37 weeks | 5514 (95) | 687 (92) | | | |
| | < 37 weeks | 300 (5) | 59 (8) | 0.010 | 1.5 (1.1-2.1) | |

Supplementary Table C. Fully adjusted model (original plus imputed data n= 6560).

*Because of coloration, 'prolonged snoring' was chosen to be entered in to the model over 'snoring' and 'early snoring' due to a higher univariate OR (odds ratio). ^R Reference category COM = chronic otitis media

CI = confidence interval