Sensorineural hearing impairment among preterm children - a Norwegian population-based study

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Abstract

Objective: To investigate the risk for sensorineural hearing impairment (SNHI) in preterm infants, and to what extent the risk is attributed to perinatal morbidities and therapies.

Design: Population-based cohort study using data from several nationwide registries.

Setting: Norwegian birth cohort 1999-2014, with data on SNHI until 2019.

Participants: 60 023 live-born preterm infants, divided in moderate-late preterm (MLP) infants (32-36 weeks), very preterm (VP) infants (28-31 weeks) and extremely preterm (EP) infants (22-27 weeks), and a reference group with all 869 797 term-born infants from the study period.

Main outcome measures: SNHI defined by selected ICD-10 codes, recorded during minimum five years observation period after birth.

Results: The overall SNHI prevalence in the preterm cohort was 1.4% compared to 0.7% in the reference group. The adjusted risk ratios (95% confidence intervals) for SNHI were 1.7 (1.5-1.8) in MLP-infants, 3.3 (2.8-3.9) in VP-infants and 7.6 (6.3-9.1) in EP-infants. Among EP-infants, decreasing gestational age was associated with a steep increase in the risk ratio of SNHI reaching 14.8 (7.7-28.7) if born at 22-23 weeks gestation. Among the VP- and MLP-infants, mechanical ventilation and antibiotic therapy had strongest association with increased risk of SNHI, but infants not receiving these therapies remained at increased risk. Among EP-infants intracranial haemorrhage increased the already high risk for SNHI. We found no signs of delayed or late-onset SNHI in preterm infants.

Conclusion: Preterm birth is an independent risk factor for SNHI. Invasive therapies and co-morbidities increase the risk, predominantly in infants born after 28 weeks gestation.

What is already known on this topic?

- Preterm infants are at higher risk for hearing impairment than infants born at term.
- Many of the perinatal morbidities associated with preterm birth and their treatments are also identified as separate risk factors for hearing impairment.
- To what extent the risk for hearing impairment in the preterm population is associated with preterm birth itself, or by associated perinatal morbidity, is poorly clarified.

What this study adds?

- The risk for SNHI increased with decreasing gestational age, and most markedly among the most immature infants born before 28 weeks of gestation.
- Invasive therapies and co-morbidities increased the risk for SNHI, but predominantly in preterm infants born after 28 weeks gestation.

How this study might affect research, practice, or policy

- Early identification of hearing impairment in preterm infants is important for hearing habilitation in this vulnerable group.
- Increased awareness and information on the risk for hearing impairment in extremely preterm infants is important when counselling parents and for audiological surveillance programs.

Introduction

Children born preterm are at increased risk for hearing impairment, a major and permanent disabling condition. [1,2] Early identification of childhood hearing impairment is of great importance for speech and language outcome.[3,4] Thus, a better understanding of the risks of hearing impairment in preterm infants can aid early identification and hearing habilitation in this vulnerable population.

Reported prevalence of hearing impairment in preterm infants varies between studies.[5–8] As for most neurodevelopmental outcomes, the prevalence seems to increase with decreasing gestational age[5,7], but many studies have focused only on extremely preterm infants.[6,9,10] To what extent more moderate preterm birth represent an independent risk factor for hearing impairment, or if the risk is caused by other perinatal morbidities or treatments associated with preterm birth, is not well clarified. Several studies report that preterm infants with hearing impairment had more extensive intensive care treatment than those without, which could imply that cumulative and co-incident risk factors are more important than individual ones.[11,12]

To confirm a hearing impairment diagnosis in a preterm infant is diagnostically challenging. Newborn hearing screening test are less specific in preterm versus term born infants.[13,14] Auditory function in preterm infants is also reported to be more unstable and may both improve and deteriorate after the newborn period.[6,15–19] It is therefore essential to have long-term data on hearing outcomes when assessing risk for hearing impairment in preterm children.

In this study we evaluate the risk for sensorineural hearing impairment (SNHI) in a Norwegian population-based cohort of preterm infants born between 1999 and 2014. We used national patient registry data, with access to SNHI-diagnoses recorded during minimum five years observation period after birth.

Methods

Data sources, linkage, and ethical approval

Data for this study was obtained from five compulsory Norwegian national health and social registries. All registries were updated through 2019 and the unique 11-digit personal identification number from the mother and the infant was used to link data between registers. The Medical Birth Registry of Norway (MBRN) contains prospectively collected data on pregnancy, delivery, maternal and neonatal health.[20,21] The Norwegian Patient Registry (NPR), established in 2008, contains diagnoses (International Classification of Diseases, 10th Revision-ICD-10) reported from both public and private health care providers. Reimbursement for both inpatient and outpatient care is based on automatic reports of diagnostic and procedural codes to the NPR, leading to high completeness of data. The Norwegian National Insurance Scheme (NIS) is the public social security system in Norway and provides financial compensation for illness-related expenses, without regard to wealth or income. Everyone with diagnoses, including hearing impairment, entitled to financial support is recorded in NIS with ICD codes. The Norwegian Cause of Death registry include data for time and cause of death and Statistics Norway contains data on education and immigration status for parents. The current study was approved by the Regional Ethical Committee for medical and health research ethics (REK nr. 2018/1789).

Study population

We included all live-born infants in Norway over the 16-year period from January 1999 to December 2014. Gestational age (GA) was determined by foetal ultrasound data, routinely recorded in MBRN, or if not available by data on last menstrual period. We excluded children with a birth weight Z-score for GA outside 3SD or without available 11-digit personal identification number. To ensure sufficient follow-up time for a diagnosis of hearing impairment we also excluded children who died before 2 years age (Suppl. Figure 1). All

129 term-born infants (GA ≥ 37 weeks), including those who had been admitted a neonatal unit for
130 treatment, constituted the reference population.

131 **Outcomes and definitions**

132 The main outcome was SNHI defined by selected ICD-10 codes registered in either the NPR
133 (H90.3-5) or the NIS. To avoid potential false positive cases, a diagnosis of SNHI had to be
134 recorded minimum twice in the NPR to be registered as a SNHI-case. From the NIS we
135 included a broader range of ICD-10 codes for hearing impairment, including those for
136 conductive, mixed, and unspecified hearing loss. This was done because explorative analysis
137 of ICD-10 diagnoses for hearing impairment registered in the NIS revealed that most codes
138 for hearing impairment were coded as "unspecific", probably reflecting a focus on the degree
139 of disability and not diagnostic code accuracy. Information on the diagnostics methods used to
140 detect SNHI was not included in NPR/NIS. However, based on common clinical practice and
141 guidelines[22], it is reasonable to assume that brain stem audiometry was used in infants and
142 toddlers, and pure tone audiometry in older children. Universal newborn hearing screening
143 was implemented in Norway in 2008, and hearing is also assessed regularly in all Norwegian
144 children during visits at public child health clinics. A complete list of the ICD-10 diagnoses
145 for hearing impairment, and the number of cases included from the NPR and the NIS, is
146 presented in Supplementary Table 1.

147 **Exposures, confounders, mediators, and covariates**

148 The main exposure of interest in this study was preterm birth, mainly subclassified in the
149 following three groups: i) moderate-late preterm (MLP) infants (GA 32-36 weeks), ii) very
150 preterm (VP) infants (GA 28-31 weeks) and iii) extremely preterm (EP) infants (GA 22-27
151 weeks). We included variables defined as confounders, mediators, and covariates. The
152 maternal variables were daily smoking early in pregnancy, immigrant status, parental
153 consanguinity, educational level, mode of delivery and prolonged (> 24 hours) rupture of

membranes (PROM). Neonatal variables included sex, birth weight (BW) and length, small for GA (SGA) defined as birthweight < 10 percentile, antibiotic therapy, intracranial haemorrhage, jaundice therapy, non-invasive respiratory support, and mechanical ventilation.

Statistical analysis

All statistical analyses were performed using the SPSS software (28.0.1.0). Results are presented as proportions, means with standard deviations (SD) or medians with interquartile range (IQR), as appropriate. Comparisons of groups were performed with chi-square and non-parametric tests. Two-tailed P-values < 0.05 were considered statistically significant.

To evaluate the association between SNHI and the exposure groups of interest we used log-binomial regression analysis. Based on the literature, we identified possible confounders and mediators[23,24] and drew a directed acyclic graph (DAG) (Suppl. Figure 2). Foetal growth restriction was considered a possible confounder. Antibiotic therapy (as a proxy for a possible infection and/or ototoxic effects), intracranial haemorrhage, jaundice therapy, non-invasive respiratory support and mechanical ventilation were considered as mediators. To evaluate whether the associations between mediators, covariates and SNHI vary by the degree of prematurity, we performed stratified univariable log-binomial regression analyses within all subgroups. Then we performed log-binomial regression analysis in two steps, with adjustment for SGA in the second step. We did not perform a formal mediation analysis as we identified strong interactions between the exposure and mediators (Suppl. Table 2), and because the effect of mediators varied substantially between all subgroups. We present crude and adjusted risk ratios (aRR) with 95% confidence interval (CI).

Results

During the 16-year study period we included 60 023 preterm infants (53% male) and a reference group with 869 797 term-born infants (51.2% male). In the preterm cohort, 3.4% (n=2 065) were EP-infants, 10.3% (n= 6 192) were VP-infants and 86.3% (n=51 766) were MLP-infants. Table 1 displays maternal and infant characteristics according to the three main groups of preterm birth and the reference group. Rates of mechanical ventilation, antibiotic treatment and intracranial haemorrhage markedly increased with decreasing GA.

The SNHI-prevalence in the term reference group, including infants admitted to neonatal units for variable reasons, was 0.7%. In the cohort of preterm infants, the overall SNHI- prevalence was 1.4%. The prevalence increased with decreasing GA and was 5.2% among EP-infants and as high as 10% in infants born at 22-23 weeks gestation. Among EP-infants, the SNHI-prevalence was higher in boys than girls (6.2% vs 4.2%, p= 0.04), but there was no sex difference in SNHI-prevalence among VP- and MLP-infants (Supplementary Table 3). The SNHI-prevalence was similar in all three groups of preterm infants when comparing those born in the first (1999-2006) versus the second (2007-2014) 8-year epoch (Supplementary Table 4). The median (IQR) age at first-time diagnosis of SNHI was lower in EP-infants (1(0-4) year) and VP-infants EP-infants (1(0-4.5) year) compared to MLP- and term-born infants (4 (1-6) years), $p < 0.002$. The percentage distribution of age at first-time SNHI-diagnosis is displayed in Figure 1.

In the univariable, unadjusted analyses, intracranial haemorrhage was the only variable associated with increased risk of SNHI in the EP-infants (Table 2). Among the VP- and MLP-infants several variables, including delivery by caesarean section, SGA, intracranial haemorrhage and antibiotic therapy and mechanical ventilation, were associated with increased risk of SNHI (Table 2). For the VP- and MLP-infants we subsequently investigated the risk of SNHI in more “healthy” infants who neither received antibiotic therapy nor

mechanical ventilation. The SNHI-prevalence was then 1.6% in VP-infants and 1.0% in MLP-infants, which is still higher than a prevalence at 0.6 % in the term reference group, when excluding infants admitted to a NICU, $p < 0.0001$.

Table 3 displays crude and adjusted RRs for SNHI in all three groups of preterm infants. The crude RRs for SNHI increased from 1.7 (1.6-1.9) in MLP-infants, to 3.5 (3.0-4.1) in VP-infants and 7.9 (6.5-9.5) in EP-infants. After adjusting for SGA, the results remained similar. Figure 2 displays aRRs (95% CI) for SNHI in infants from 22 to 36 weeks GA. There was a steep increase in the risk of SNHI in the two most immature groups with aRRs at 11.8 (9.0-15.3) for infants with GA 24-25 weeks and 14.8 (7.7-28.7) for infants with GA 22-23 weeks.

Discussion

In this national cohort of more than 60 000 preterm infants, born between 1999 and 2014, and followed up through 2019, there was a significantly increased risk for SNHI in preterm compared to term infants, and the risk increased markedly in the most immature infants. In infants born after 28 weeks gestation, variables associated with increased perinatal morbidity, and in particular need for mechanical ventilation and antibiotic therapy, increased the risk for SNHI. In contrast, among the most immature infants only the presence of intracranial haemorrhage clearly increased the already high baseline risk of SNHI.

In our study the overall prevalence of SNHI among preterm infants was more than double that of the term reference group, but the risk for SNHI was around 15 times higher in the most immature babies. Several studies report higher rates of hearing impairment among preterm infants than in the general newborn population.[6,23,25] Most studies also demonstrate a similar clear trend, as in our study, with increasing rates of hearing impairment with decreasing GA [5,7,25,26] and BW.[27,28] Our prevalence results are in line with two recent large

studies from Poland and The Netherlands reporting hearing impairment rates ranging from 1-2% in preterm infants with GA 31-32 weeks and increasing to 7-11% in those with GA 24-25 weeks.[5,7] However, rates of hearing impairment in preterm infants vary between studies due to variations in the diagnostic methods used and the definitions of hearing impairment.[5,6,26–29] SNHI-prevalence among EP-infants can also be affected by mortality rates of the sickest babies at highest risk for SNHI.[6] However, we found similar rates of SNHI in preterm infants born in the first and last 8-year epoch of our study cohort, concomitantly with stable survival rates for EP-infants in Norway during the same time period.[30] Two previous Norwegian historical cohort studies spanning from 1967 to 1998 also reported a 6-8-fold increased risk of hearing impairment in very low BW infants compared to normal weight term control infants.[27,28]

Sufficient follow-up time is important to detect progressive[31] and/or late-onset hearing impairment, which is reported in 13-33% of children with hearing impairment.[32,33] In contrast to previous reports[16,34], we found no signs of increased risk for late-onset SNHI in our preterm cohort. In fact, the EP- and VP-infants were younger when a SNHI-diagnosis was established than more mature infants. This could also reflect raised awareness of possible adverse neurodevelopmental and hearing outcomes among preterm infants leading to closer follow-up of this population.[35]

In preterm infants many co-morbidities and therapies are identified as risk factors for hearing impairment.[8,24,36,37] The contribution of these risk factors to SNHI may differ,[23] but cumulative effects appear common.[11,12] The large UK Millennium Cohort Study reported an association between parental-reported neonatal illness and risk for hearing impairment in school age, but no association to GA.[29] In our study neonatal illness data were more detailed and we found different results. The pathophysiological pathways in hearing impairment associated with preterm birth are not well clarified. A central question is to what extent the

risk is associated with preterm birth itself or by its associated morbidity. The time before 27 weeks of gestation is a critical period in auditory development with rapid growth of cochlea and the auditory nerve.[38] We speculate that SNHI in the most immature infants is causally linked to their immature auditory system, and that associated morbidities and invasive therapies have a relatively higher contribution in the causal pathways of SNHI in preterm infants with higher gestational age.[12] In the EP-infants, intracranial haemorrhage was the only independent risk factor for SNHI, an association also reported by others.[39] In contrast, among preterm infants born after 28 weeks gestation mechanical ventilation and antibiotic therapy were identified as strong independent predictors for SNHI, in line with many others.[8,9,24,40] Still, rates of SNHI remained significantly higher in VP- and MLP-infants not receiving these therapies when compared to term infants. Thus, overall our study indicates that that preterm birth across all GAs is an independent risk factor for SNHI.

Our study has several strengths. It covers a population-based cohort of more than 60 000 preterm infants with data from several validated national health registries, including data on neonatal morbidity and treatment. The cohort spans the range from 22 to 36 weeks gestation, making it possible to assess differences in risk of SNHI across this range of prematurity. We used DAGs to select possible confounders for the regression analysis, but residual confounding cannot be excluded. The recorded SNHI diagnoses were established five years or longer after study participants were born, which made it possible to detect potentially late-onset cases of hearing impairment. As for similar cohort studies, several limitations also apply. First, we did not have data on treatment duration for mechanical ventilation and antibiotics, we lacked data on exposure to other drugs and noise, and we did not have information on SNHI in parents/siblings. Second, ICD-10 codes do not include criteria for hearing thresholds in decibel or affected frequencies and do therefore not assess the type or severity of SNHI. Procedural codes for hearing aids and cochlear implants would have

provide better data to assess functional loss of hearing impairment but were not available for this study. Third, the high rate of co-morbidities and invasive therapies in the relatively small group of EP-infants may have resulted in lack of statistical power to detect possible associations. Finally, preterm infants are also at increased risk for impaired central auditory processing function[41], but such complex data were not available for this study.

CONCLUSION

Our study indicates that preterm birth is an independent risk factor for later SNHI. Invasive therapies and co-morbidities increased the risk for SNHI, but predominantly in preterm infants born after 28 weeks gestation. Infants born before 28 weeks gestation had high a risk for SNHI, and only the presence of intracranial haemorrhage increased the high baseline risk.

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Data sharing statement: The study has utilized Norwegian governmental registries and legal restrictions do not permit the authors to share these data.

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Competing interest: None

Contributorship statement: Dagny Hemmingsen conceptualized and designed the study, did the initial analysis, had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, wrote the first draft of the manuscript, and revised the final manuscript. Dag Moster had a central role in acquisition of data, extracted and linked variables from the different data sources, took part in designing the study and writing of the manuscript. Bo Engdahl gave substantial contributions to the design of the work, took part in analysis of data and writing of the manuscript. Claus Klingenberg conceptualized and designed the study, supervised and coordinated data collection, gave directions in all phases of the study, had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis and revised the final manuscript. All authors approved the final manuscript to be published and agrees to be accountable for all aspects of the work.

Ethics approval: The study was performed in line with the principles of the Declaration of Helsinki. The study and linkage between the five registries were approved by the Regional Ethical Committee for medical and health research ethics (REK nr. 2018/1789).

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Figure Legends

Figure 1. Age (years) at first-time diagnosis of sensorineural hearing impairment in preterm and term infants born in Norway 2008-2014 and alive at two years of age.

EP, extremely preterm; VP, very preterm; MLP, moderate-late preterm

Data based on NPR diagnoses which are available for infants from birth since 2008.

Figure 2 Adjusted* risk ratios (95% CI) for sensorineural hearing impairment according to weeks of gestation in preterm children born in Norway from 1999 through 2014.

*Adjusted for SGA

Reference to term-born infants.

Table 1. Study cohort of infants born in Norway 1999-2014 and alive at two years of age - maternal and infant characteristics.

Norwegian birth cohort 1999-2014	GA 22 - 27 weeks N = 2 065	GA 28 - 31 weeks N = 6 192	GA 32 - 36 weeks N = 51 766	GA > 36 weeks N = 869 797
	Extremely preterm infants	**Very preterm infants**	**Moderate-late preterm infants**	**Term born Reference group**
Maternal characteristics				
Smoking at the beginning of pregnancy *	269 (13.0)	868 (14.0)	6 955 (16.2)	99 513 (11.4)
Low education (high school or less)	1 081 (52.3)	3 216 (51.9)	25 800 (49.8)	394 336 (45.2)
Parental consanguinity	21 (1.0)	64 (1.0)	541 (1.0)	9 053 (1.0)
Immigrant status of parents	298 (14.4)	735 (11.9)	5 811 (11.2)	106 651 (12.3)
Prolonged rupture (> 24 h) of membranes	402 (19.5)	1 045 (16.9)	6 779 (13.1)	50 938 (5.9)
Caesarean section	1 239 (59.6)	4 302 (69.5)	19 510 (37.7)	123 823 (14.2)
Infant characteristics				
Birth weight (g)	840 (770-990)	1 400 (1 180-1 625)	2 540 (2 185-2 880)	3 582 (3 260- 3915)
Birth length (cm)	34 (32-36)	40 (37-41)	46 (45-48)	50 (49-52)
Gestational age (weeks)	26 (25-27)	30 (29-31)	35 (34-36)	40 (39-41)
Small for gestational age	337 (16.3)	1 222 (19.7)	8 821 (17.0)	71 665 (8.2)
Male	1 068 (51.7)	3 297 (53.2)	27 196 (52.5)	445 643 (51.2)
Apgar 5-min score **	8 (6-9)	9 (8-9)	9 (9-9)	10 (9-10)
Apgar 5-min score categories				
0-3	99 (4.8)	98 (1.6)	257 (0.5)	1 477 (0.2)
4-6	510 (24.7)	585 (9.4)	1 295 (2.5)	6 359 (0.7)
7-10	1 398 (67.7)	5 453 (88.1)	50 058 (96.7)	761 700 (99.0)
Intracranial haemorrhage	533 (25.8)	492 (7.9)	280 (0.5)	606 (0.1)
Jaundice therapy	1 596 (77.3)	4 149 (67.0)	19 465 (37.6)	38 675 (4.4)
Antibiotic therapy	1 629 (78.9)	3 393 (54.8)	5 606 (10.8)	17 536 (2.0)
Non-invasive respiratory support	1 571 (76.1)	3 938 (63.6)	6 550 (12.7)	4 966 (0.6)
Mechanical ventilation	1 348 (65.3)	1 318 (21.3)	1 033 (2.0)	1 799 (0.2)
Admission to NICU	2 060 (99.8)	6 172 (99.7)	29 776 (57.5)	60 647 (7.3)
Hearing Impairment	108 (5.2)	143 (2.3)	597 (1.2)	5 794 (0.7)

All data are numbers and proportions (%) or median and interquartile range (IQR) if not otherwise stated.

GA, gestational age; NICU, neonatal intensive care admission. *Data missing for 15.9% of mothers. ** Data missing for 0.2% of the total population,

Table 2. Univariable analysis and risk ratios (95 % CI) for sensorineural hearing impairment in preterm and term children born in Norway 1999-2014 (N=60 024)

	Extremely preterm infants GA 22 - 27 weeks N = 2 065	**Very preterm infants** GA 28 - 31 weeks N = 6 192	**Moderate-late preterm infants** GA 32 - 36 weeks N =51 766	**Term reference group** GA > 36 weeks N = 869 797
	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)
Apgar 5 min score < 7 min	1.0 (0.7-1.5)	**1.6 (1.1-2.6)**	**3.1 (2.3-4.1)**	**2.3 (2.0-2.8)**
Small for gestational age	1.3 (0.8-2.1)	**1.6 (1.1-2.3)**	**1.6 (1.3-1.9)**	**1.5 (1.3-1.6)**
Caesarean section	0.8 (0.5-1.1)	**1.5 (1.03-2.25)**	**1.3 (1.1-1.5)**	**1.1 (1.1-1.2)**
Prolonged rupture of membranes	0.6 (0.3-1.0)	0.6 (0.4-1.0)	0.9 (0.7-1.1)	1.0 (0.9-1.1)
Intracranial haemorrhage	**2.0 (1.4-2.9)**	1.6 (0.95-2.57)	**4.7 (2.9-8.4)**	**4.2 (2.6-6.7)**
Antibiotic therapy	1.0 (0.6-1.6)	**1.7 (1.2-2.5)**	**2.1 (1.7-2.5)**	**2.5 (2.3-2.8)**
Non-invasive respiratory support	0.9 (0.6-1.4)	**1.4 (0.96-1.99)**	**1.5 (1.2-1.9)**	**3.5 (2.9-4.2)**
Mechanical ventilation	1.4 (0.9-2.1)	**2.4 (1.7-3.3)**	**5.0 (3.8-6.5)**	**6.0 (4.8-7.5)**
Jaundice therapy	0.8 (0.6-1.3)	1.2 (0.9-1.8)	**1.3 (1.1-1.5)**	**1.4 (1.3-1.6)**
Parental consanguinity	1.9 (0.5-7.0)	**3.5 (1.5-8.2)**	1.0 (0.4-2.1)	**1.8 (1.5-2.2)**

GA, gestational age; RR, risk ratio

Table 3. Prevalence, crude, and adjusted risk ratio (RR) for sensorineural hearing impairment in children born in Norway 1999 -2014 (N=60 024)

Group description	**Hearing impairment N (%)**	**Crude risk ratio (95 % CI)**	**Adjusted risk ratio* (95 % CI)**
Term born, reference, GA > 36 weeks. N=869 797	5 749 (0.7)	Reference	Reference
Moderate-late preterm infants, GA 32- 36 weeks N=51 766	597 (1.2)	1.7 (1.6-1.9)	1.7 (1.5-1.8)
Very preterm infants, GA 28-31 weeks N=6 192	143 (2.3)	3.5 (3.0-4.1)	3.3 (2.8-3.9)
Extremely preterm infants, GA 22-27 weeks N=2 065	108 (5.2)	7.9 (6.5-9.5)	7.6 (6.3-9.1)

* Adjusted for small for gestational age

GA, gestational age

Figure 1

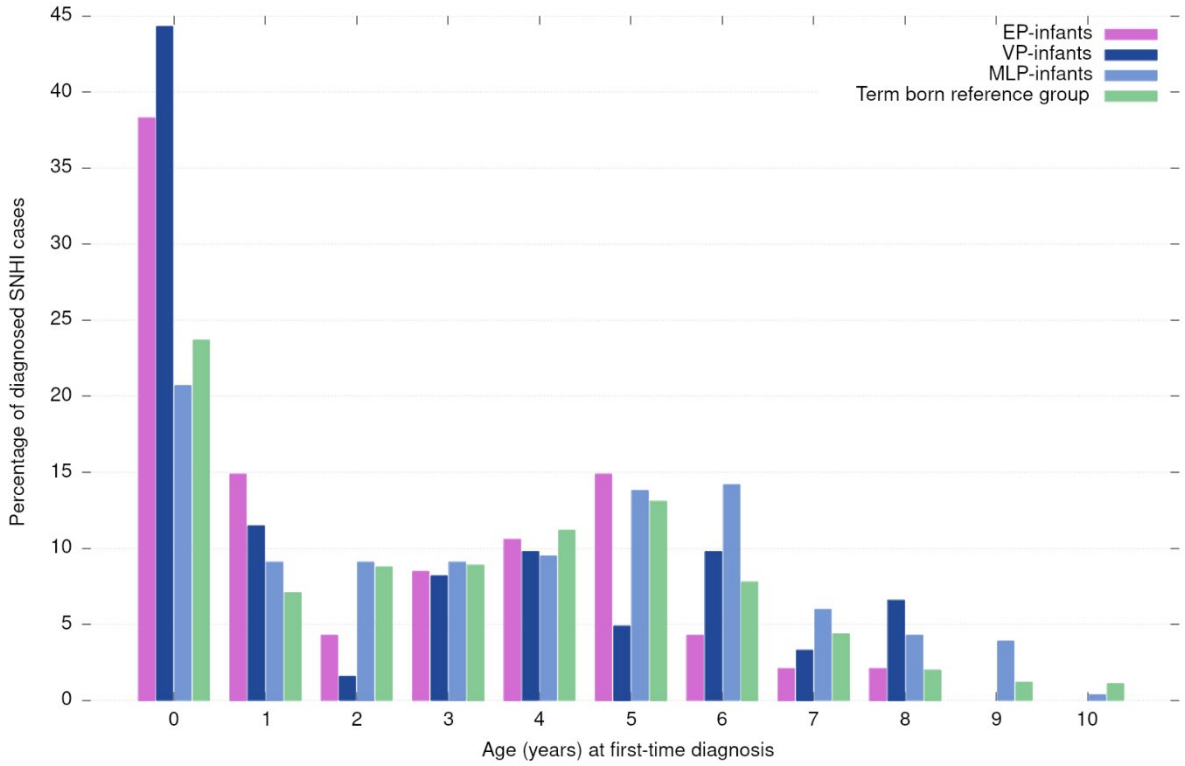
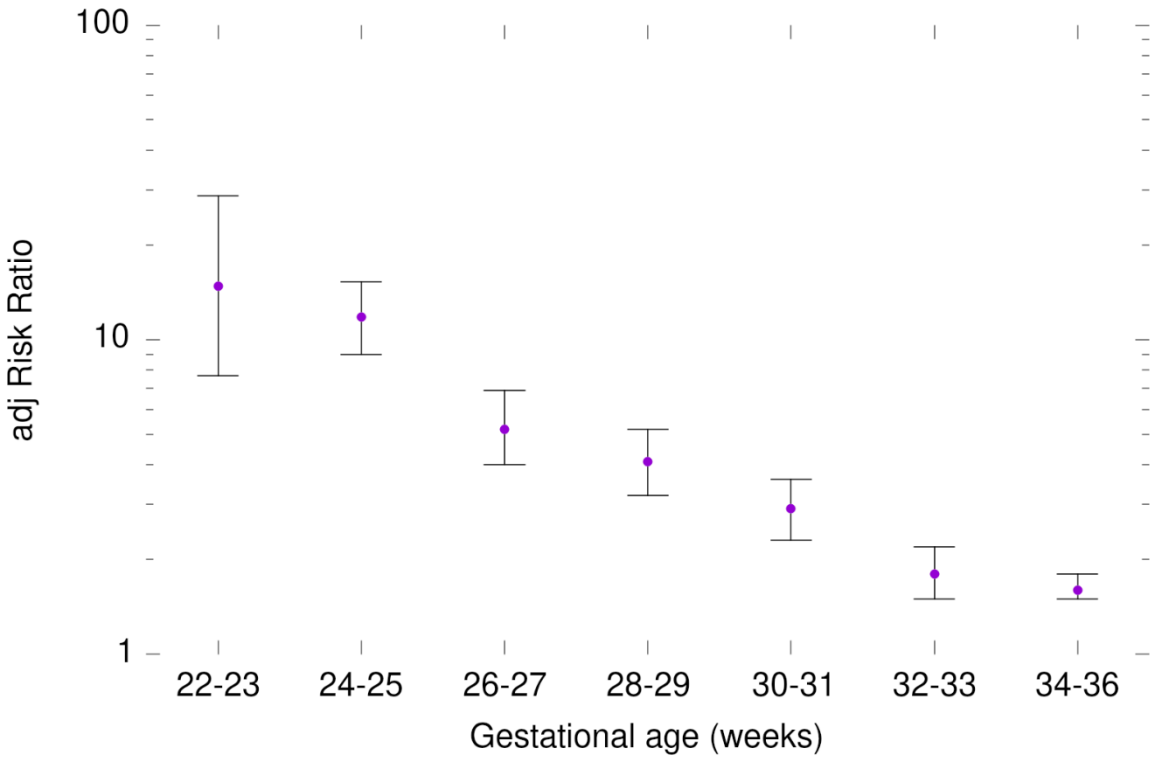

EP-infants
VP-infants
MLP-infants
Term born reference group
Percentage of diagnosed SNHI cases
45
40
35
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
9
10
Age (years) at first-time diagnosis

Figure 2


100
10
1
adj Risk Ratio
22-23
24-25
26-27
28-29
30-31
32-33
34-36
Gestational age (weeks)

Suppl. Table 1. Diagnostic codes for hearing impairment in ICD-10 and included cases from the Norwegian patient registry (NPR) and the Norwegian national insurance scheme (NIS).

ICD-10 Diagnostic codes		**Cases included from NPR***	**Cases included from NIS****	**Cases registered in both NPR and NIS**	**Total number of cases included.**
H 90.0	Conductive hearing loss, bilateral	No	No		
H 90.1	Conductive hearing loss, unilateral	No	No		
H 90.2	Conductive hearing loss, unspecified	No	No		
H 90.3	Sensorineural hearing loss, bilateral	Yes	Yes		
H 90.4	Sensorineural hearing loss, unilateral	Yes	Yes		
H 90.5	Sensorineural hearing loss, unspecified	Yes	Yes		
H 90.6	Mixed conductive and sensorineural hearing loss, bilateral	No	Yes		
H 90.7	Mixed conductive and sensorineural hearing loss, unilateral	No	Yes		
H 90.8	Mixed conductive and sensorineural hearing loss, unspecified	No	Yes		
H 91.3	Deaf mutism, not elsewhere classified	No	Yes		
H 91.8	Other specified hearing loss	No	Yes		
H 91.9	Hearing loss, unspecified	No	Yes		
TOTAL		5 339	433	363	5 409

Suppl. Table 2. Binomial regression analysis with interaction terms for antibiotics, mechanical ventilation, intracranial haemorrhage and jaundice. All Risk Ratio analyses are adjusted for small for gestational age.

Gestational age categories	**Antibiotic treatment**				Interaction term	P values
	YES	NO	YES	NO		
	Prevalence SNHI (%)	Prevalence SNHI (%)	Risk Ratios (95% CI)	Risk Ratios (95% CI)		
Reference (GA > 36 w)	287 (1.6)	5 507 (0.6)	1	1		
MLPI	119 (2.1)	478 (1.0)	1.26 (1.02-1.55)	1.50 (1.4-1.7)	1.23 (0.97-1.54)	0.085
VPI	97 (2.9)	46 (1.6)	1.66 (1.30-2.08)	2.40 (1.8-3.2)	1.46 (1.01-2.11)	**0.042**
EPI	85 (5.2)	23 (5.3)	3.08 (2.40-3.90)	7.90 (5.3-11.8)	2.56 (1.60-4.07)	**< 0.001**
Gestational age categories	**Mechanical ventilation**				Interaction term	P values
	YES	NO	YES	NO		
	Prevalence SNHI (%)	Prevalence SNHI (%)	Risk Ratios (95% CI)	Risk Ratios (95% CI)		
Reference (GA > 36 w)	71 (3.9)	5 723 (0.7)	1	1		
MLPI	55 (5.3)	542 (1.1)	1.34 (0.95-1.89)	1.08 (1.05-1.10)	1.16 (0.81-1.66)	0.40
VPI	56 (4.2)	87 (1.8)	1.05 (0.74-1.48)	1.20 (1.13-1.31)	2.46 (1.65-3.69)	**< 0.001**
EPI	78 (5.8)	30 (4.2)	1.46 (1.06-1.99)	1.70 (1.47-2.00)	4.23 (2.60-6.77)	**< 0.001**
Gestational age categories	**Intracranial haemorrhage**				Interaction term	P values
	YES	NO	YES	NO		
	Prevalence SNHI (%)	Prevalence SNHI (%)	Risk Ratios (95% CI)	Risk Ratios (95% CI)		
Reference (GA > 36 w)	17 (2.8)	5 777 (0.7)	1	1		
MLPI	15 (5.4)	582 (1.1)	1.80 (0.91-3.55)	1.57 (1.44-1.71)	0.91 (0.46-1.80)	0.79
VPI	17 (3.5)	126 (2.2)	1.20 (0.62-2.32)	2.99 (2.52-3.56)	2.64 (1.33-5.23)	**0.005**
EPI	44 (8.3)	64 (4.2)	2.88 (1.67-4.98)	5.72 (4.50-7.28)	2.10 (1.16-3.82)	**0.015**
Gestational age categories	**Jaundice**				Interaction term	P values
	YES	NO	YES	NO		
	Prevalence SNHI (%)	Prevalence SNHI (%)	Risk Ratios (95% CI)	Risk Ratios (95% CI)		
Reference (GA > 36 w)	355 (0.9)	5 439 (0.7)	1	1		
MLPI	260 (1.3)	337 (1.0)	1.42 (1.21-1.67)	1.18 (1.09-1.27)	1.09 (0.89-1.32)	0.41
VPI	102 (2.5)	41 (2.0)	2.58 (2.08-3.21)	1.67 (1.30-2.13)	1.15 (0.79-1.67)	0.47
EPI	80 (5.0)	28 (6.0)	5.39 (4.26-6.84)	3.82 (2.74-5.32)	1.62 (1.05-2.50)	**0.03**

GA, gestational age; SNHI, sensorineural hearing impairment; w, weeks; EPI, Extremely preterm infants; VPI, Very preterm infants; MLPI, Moderate and late preterm infants

Suppl. Table 3. Sensorineural hearing impairment, divided by sex, in children born in Norway from 1999 through 2014

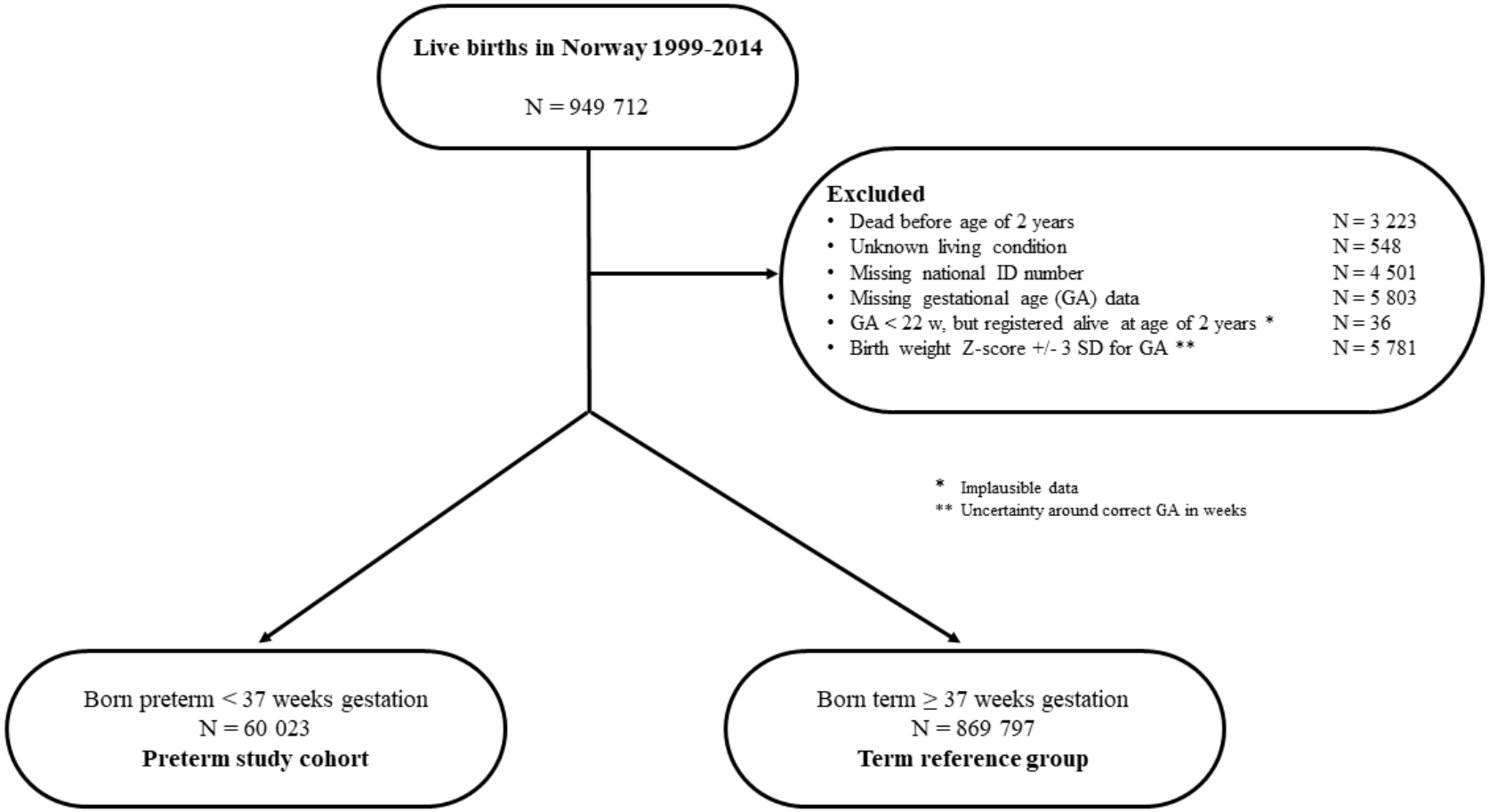
Group description	Gender distribution	MALE	FEMALE	Chi Square P-value	MALE	FEMALE
		Hearing impairment N %	Hearing impairment N (%)		Adjusted RR * (95% CI)	Adjusted RR * (95% CI)
Reference group GA > 36 weeks and not admitted N=869 797	Male: 51.2% (N=445 643)	3 021(0.7)	2 773 (0.7)		Not applicable	Not applicable
Extremely preterm infants GA 22-27 weeks N=2 065	Male: 51.7% (N=1 068)	66 (6.2)	42 (4.2)	4.03 **P= 0.045**	8.7 (6.9-11.1)	6.3 (4.7-8.4)
Very preterm infants GA 28-31 weeks N=6 192	Male: 53.2% (N=3 297)	72 (2.2)	71 (2.5)	0.49 P=0.48	3.1 (2.4-3.9)	3.7 (2.8-4.5)
Moderate and late preterm infants GA 32- 36 weeks N=51 766	Male: 52.5% (N=27 196)	337 (1.2)	260 (1.1)	3.7 P=0.054	1.8 (1.6-2.0)	1.5 (1.4-1.8)

*Adjusted for small for gestational age

Suppl. Table 4. Comparison of sensorineural hearing impairment prevalence in the first and second 8-year epoch of the 16-year birth cohort

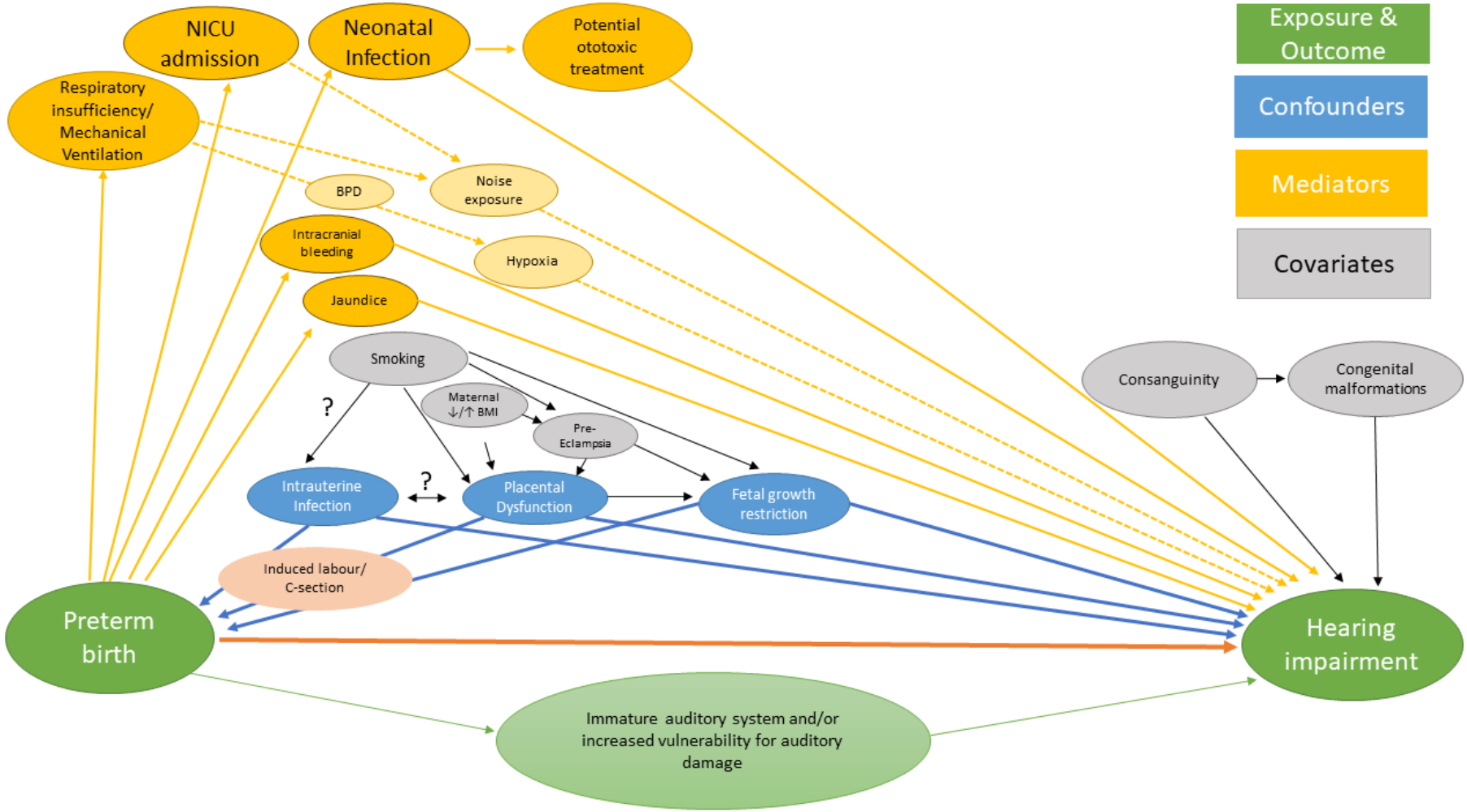
Extremely preterm infants, < 28 weeks gestation	**N**	**Sensorineural hearing impairment N (%)**
Birth year		
1999-2006	1 072	54 (5.0%)
2007-2014	993	54 (5.4%)
Total cohort (1999-2014)	2 065	108 (5.2%)
Very preterm infants, 28-31weeks gestation	**N**	**Sensorineural hearing impairment N (%)**
Birth year		
1999-2006	3 175	69 (2.1%)
2007-2014	3 017	74 (2.5%)
Total cohort (1999-2014)	6 192	143 (2.3%)
Extremely preterm infants, < 28 weeks gestation	**N**	**Sensorineural hearing impairment N (%)**
Birth year		
1999-2006	26 180	318 (1.2%)
2007-2014	25 586	279 (1.1%)
Total cohort (1999-2014)	51 766	579 (1.1%)

Suppl. Figure 1. Study cohort flow diagram.



BW, birth weight; GA, gestational age; ID, identification; NICU, Neonatal Intensive Care Unit,

Suppl. Figure 2. Directed acyclic graph on associations between preterm birth and hearing impairment.



BMI, Body Mass Index; BPD, bronchopulmonary dysplasia; C-section, caesarean section; NICU, Neonatal Intensive Care Unit
Dotted lines indicate an assumed causal relationship between mediators and the outcome.