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Neonatal risk factors for hearing impairment

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In memoriam

Signe Dorthea Hemmingsen

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// Dagny

List of Papers

Paper I

Hemmingsen D, Mikalsen C, Hansen AR, Fjalstad JW, Stenklev NC, Klingenberg C. Hearing in Schoolchildren After Neonatal Exposure to a High-Dose Gentamicin Regimen. Pediatrics. 2020 Feb;145(2) [1].

Paper II

Hemmingsen D, Moster D, Engdahl B, Klingenberg C. Hearing impairment after asphyxia and neonatal encephalopathy: a Norwegian population-based study. Eur J Pediatr. 2024 Mar;183: 1163-1172 [2].

Paper III

Hemmingsen D, Moster D, Engdahl B, Klingenberg C. Sensorineural hearing impairment among preterm children- a Norwegian population-based study. Arch Dis Child Fetal Neonatal Ed. 2024 Jun 11. Online ahead of print [3].

Publications not included in this thesis:

Hemmingsen D, Stenklev NC, Klingenberg C. Extended high frequency audiometry thresholds in healthy school children. Int J Pediatr Otorhinolaryngol. 2021 May;144 [4].

Rypdal V, Jørandli S, Hemmingsen D, Solbu MD, Klingenberg C. Exposure to an Extended-Interval, High-Dose Gentamicin Regimen in the Neonatal Period Is Not Associated With Long-Term Nephrotoxicity. Front Pediatr. 2021 Nov 30;9 [5]

English summary

Hearing impairment (HI) is a prevalent childhood disability with significant public health implications, impacting language and developmental outcomes if not early identified and managed. While illness in the neonatal period is a recognized risk factor for HI, less is known about the specific impacts of the different, and often interrelated morbidities and invasive treatments in neonatal intensive care. This thesis aimed to study and better clarify these associations, focusing on three central exposures and their associated risks of childhood sensorineural hearing impairment (SNHI). **Paper I** is a clinical follow-up study with detailed measurements of hearing in school children who had been treated with gentamicin, a potential ototoxic antibiotic, as neonates. **Paper II** and **Paper III** are population-based registry studies covering all Norwegian births from 1999 to 2014. Here we investigated the associations between perinatal asphyxia/neonatal encephalopathy (**Paper II**) and preterm birth (**Paper III**), and risk of a SNHI-diagnosis in childhood, using data from several national registers.

In **Paper I** we found no association between neonatal gentamicin treatment and hearing thresholds in school age but found that low birth weight was associated with poorer hearing thresholds. In **Paper II** and **Paper III,** we found that increasing clinical severity of perinatal asphyxia/neonatal encephalopathy and decreasing gestational age markedly increased the risk of SNHI. Around 1 out of 20 infants with moderate-severe hypoxic-ischemic encephalopathy and/or preterm infants with gestational age below 28 weeks were diagnosed with SNHI in childhood age. Invasive therapies and co-morbidities increased the SNHI-risk, particularly in infants born after 28 weeks.

The research in this thesis contributes with valuable long-term and high-quality audiological data following neonatal gentamicin treatment, indicating a low risk of ototoxic damage from this commonly used antibiotic. Furthermore, the thesis supports previous findings that asphyxia and neonatal encephalopathy, and preterm birth are significant independent risk factors for SNHI. Knowledge of the SNHI-risks in sick neonates is essential for prophylactic measures, but also important to aid early identification and rehabilitation of HI in this vulnerable population.

Norsk sammendrag

Hørselstap er en hyppig forekommende tilstand hos barn og unge, med betydelige konsekvenser i et folkehelseperspektiv, ettersom tilstanden kan ha store konsekvenser for språk- og generell utvikling dersom hørselstapet ikke oppdages raskt og adekvate tiltak igangsettes. Det er godt kjent at sykdom i nyfødtperioden gir risiko for hørselstap, men mindre kunnskap om i hvilken grad de ulike sykdomstilstander og behandlinger hos nyfødte i intensivbehandling samvirker, og påvirker den totale risikoen. Målet med denne avhandlingen har vært å bedre klarlegge assosiasjonene mellom sykelighet i nyfødtperioden og risiko for sensorinevrogent hørselstap i barnealder bedre, med fokus på tre sentrale tilstander hos syke nyfødte. **Artikkel I** er en klinisk oppfølgingsstudie med detaljerte hørselsmålinger av skolebarn som ble behandlet med gentamicin, et potensielt ototoksisk antibiotikum, i nyfødtperioden. **Artikkel II og Artikkel III** er populasjonsbaserte registerstudier som omfatter norske fødselskohorter i tidsperioden 1999 til 2014. I disse studiene undersøkte vi assosiasjoner mellom perinatal asfyksi/ neonatal encefalopati (**Artikkel II**) og prematur fødsel (**Artikkel III)**, og risiko for sensorinevrogent hørselstap i barnealder med bruk av data fra flere ulike nasjonale helseregistre. I **Artikkel I** fant vi ingen assosiasjon mellom gentamicin behandling i nyfødtperioden og høreterskler i skolealder, men vi fant at lav fødselsvekt var assosiert med dårligere høreterskler. I **Artikkel II** og **Artikkel III** fant vi at økt klinisk alvorlighetsgrad av perinatal asfyksi/ neonatal encefalopati, og lavere gestasjonsalder, ga en markant økning i risiko for sensorinevrogent hørselstap. Om lag 1 av 20 nyfødte med moderat-alvorlig hypoksisk encefalopati og/ eller født prematurt før 28 gestasjonsuke ble diagnostisert med sensorinevrogent hørselstap i barnealder. Intensiv behandling og komorbide tilstander økte risikoen for sensorinevrogent hørselstap, spesielt hos barn født etter 28 gestasjonsuker. Forskningsfunnene fra denne avhandlingen bidrar med verdifulle langtidsdata på hørsel, av høy kvalitet etter gentamicin behandling i nyfødtperioden, som indikerer en lav risiko for ototoksiske bivirkninger av et mye brukt antibiotisk legemiddel. Videre støtter avhandlingen opp om funn fra tidligere forskning om at både asfyksi/ neonatal encefalopati og prematur fødsel er selvstendige risikofaktorer for sensorinevrogent hørselstap. Kunnskap om risiko for sensorinevrogent hørselstap hos syke nyfødte er nødvendig for å kunne lage forebyggende tiltak, men også viktig for å sikre tidlig diagnostikk og habilitering av hørselstap i denne sårbare populasjonen.

List of abbreviations

ABR	Auditory brainstem response
AABR	Automated brain stem audiometry
AG	Aminoglycosides
AN	Auditory neuropathy
ANSD	Auditory neuropathy spectrum disorder
ASSR	Auditory steady-state responses
BPD	Bronchopulmonary dysplasia
BW	Birth weight
CAPD	Central auditory processing disorder
cCMV	Congenital cytomegalovirus
CI	Cochlear implant
DAG	Directed acyclic graph
DPOAE	Distortion product otoacoustic emissions
EHF	Extended high frequency
EP	Extremely preterm
GA	Gestational age
GBD	Global burden of disease study
HA	Hearing aid
HI	Hearing Impairment
HIE	Hypoxic-ischemic encephalopathy
HL	Hearing level

JCHI	Joint Committee of Infant Hearing
MBRN	Medical Birth Registry of Norway
MDD	Multiple daily dosing
MLP	Moderate-late preterm
NICU	Neonatal intensive care unit
NIS	Norwegian National Insurance Scheme
NPR	Norwegian Patient Registry
OAE	Otoacoustic emissions
ODD	Once daily dosing
OR	Odds Ratio
RDS	Respiratory distress syndrome
RR	Risk Ratio
SGA	Small for gestational age
SNHI	Sensorineural hearing impairment
SPL	Sound pressure level
TPC	Trough plasma concentration
TEOAE	Transient evoked otoacoustic emission
UNHS	Universal newborn hearing screening
VLBW	Very low birth weight
VP	Very preterm
WHO	World health organization

1. Introduction

1.1 Preface

Hearing impairment (HI) is the most common sensory deficit [6] and one of the leading causes of disability in the global population [7]. The global burden of HI is anticipated to rise significantly [8], due to demographic changes with increased life expectancy leading to a larger aging population [9]. Hearing is essential for learning spoken language, which in turn may affect social, cognitive, developmental, and educational outcomes. The childhood population is therefore especially vulnerable for unaddressed HI.

During the last 30 years, childhood mortality has decreased globally, but a corresponding improvement in non-fatal long-term complications in childhood survivors is lacking [10]. HI is one of the most common adverse long-term outcomes after intrauterine and neonatal insults [11] and is ranked as the second most common developmental disability in children under 5 years [12].

A growing body of studies show that early developmental factors affect the risk for HI later in life [13]. A better understanding of congenital and early life risk factors is important for public health measures, improving screening programs and identifying children at risk for late-onset HI [14].

This PhD thesis seeks to bring new knowledge upon how exposures in the neonatal period influence the risk for HI later in childhood. The thesis focuses on three central exposures in the neonatal period: gentamicin treatment, a drug with ototoxic potential frequently used in neonates, birth asphyxia and neonatal encephalopathy, and preterm birth.

1.2 The auditory system

1.2.1 Development of the auditory system

Embryologically, the ear has two origins; the inner ear develops from the thickened ectodermal otic placode, while the middle and external ear develop from the first and second pharyngeal arches [15]. The inner ear develops from the fourth gestational week when the otic placode invaginates to form the otocyst, a closed vesicle located within the temporal bone [16]. The otocyst divides into vestibular and cochlear parts, with the cochlear segment evolving into the

fully coiled cochlear duct by the eighth week. The organ of Corti appears within the cochlear duct at the ninth week of gestation, followed by development of hair cells and supporting cells. By 11-12th weeks the cochlear duct is surrounded by fluid and a cartilage shell. Development of the eight cranial nerve is parallel to cochlear development, with cells migrating from the otic vesicle to form the statoacoustic ganglion. The immature neurons extend fibers both toward the brainstem and the organ of Corti, establishing synaptic connections with hair cells by the end of the first trimester. Auditory nuclei and pathways in the brainstem are identifiable by 7-8th weeks of gestation [17].

In the second trimester, from week 14 to the end of week 27, the cochlea and auditory nerve undergo rapid maturation, with formation of the scala tympani and scala vestibuli, and maturation of inner and outer hair cells with formation of stereocilia. Extremely preterm babies cared for today are born during the last 4-5 weeks of this vulnerable period of cochlea and auditory nerve maturation [18]. By the end of the second semester the cochlea has a mature appearance, with exception of less developed synaptic terminals compared to the adult cochlea. In the third trimester myelination progresses from the cochlear outlet along the auditory nerve to the brainstem and thalamus. This process is parallel with the first behavioral and physiological responses to sound.

The maturation of auditory structures continues after birth and is characterized by increase in the myelin density in the auditory nerve and brainstem auditory pathways. This significant postnatal maturation is thought to explain the reduction in latency of brain stem response observed after birth [19, 20]. The development of auditory cortex is prolonged compared to other human sensory cortices which mature within the first year of life. The auditory cortex development is characterized by axonal development in the deep layers in the early childhood years and concludes with maturation of axons in the superficial layers and intracortical connections between 6-12 years of age [17].

1.2.2 Anatomy and physiology of the auditory system

The human ear serves to transmit sound from the surroundings to the central nervous system, where it is consciously perceived. It consists of three functional parts: the outer ear (with the auricle and external auditory canal leading to the tympanic membrane), the middle ear (an air-filled cavity with ossicular bones connected to the oval window in the inner ear), and the inner ear (comprising the labyrinth for balance and the cochlea for hearing) [21]. Signals from the

labyrinth and cochlea are transmitted via the vestibular and cochlear nerves, forming the eighth cranial nerve anatomically.

The cochlea is a coiled structure containing three fluid-filled compartments: scala vestibuli, scala media, and scala tympani (**Figure 1**) [21]. The basilar membrane forms the base of scala media, separating it from the scala tympani. The cochlea contains the metabolically active structure stria vascularis which produces endolymph with a high potassium level, that serves to sustain the endocochlear potential between the endolymph in the scala media and the perilymph in the scala tympani and vestibuli. The organ of Corti within the scala media contains sensory cells (hair cells) that convert mechanical sound signals into electrical signals transmitted to the auditory nerve [22]. Different frequencies stimulate distinct groups of hair cells along the basilar membrane, leading to a tonotopic organization where higher frequencies are represented at the basal turn and lower frequencies are found more apically [21]. Sound waves from the environment cause the tympanic membrane to vibrate, initiating motion in the ossicular chain and ultimately stimulating the hair cells to generate electrical signals transmitted to the brain for auditory processing.

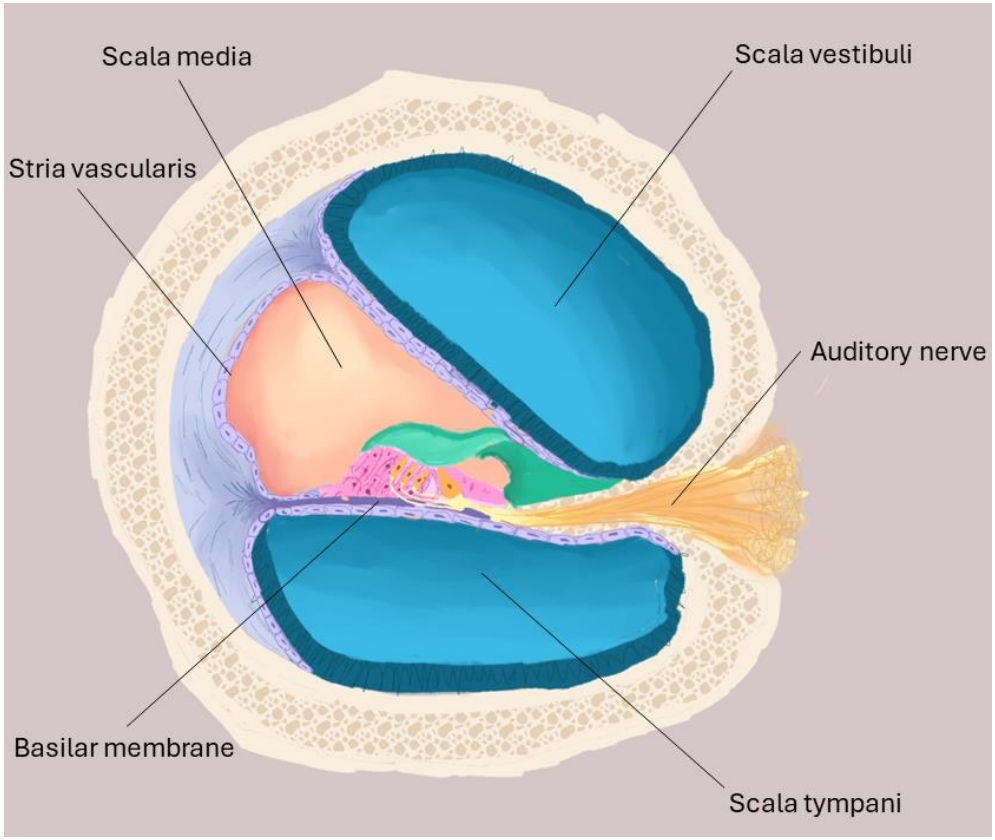


Figure 1. Cochlear anatomy. Illustration by Ingrid Sudmann

1.3 Childhood hearing impairment

1.3.1 Definitions and classifications

Hearing impairment (HI) is the inability to hear sounds at thresholds defined as normal. World Health Organization (WHO) defines HI as a hearing capability below the standard threshold level of 20 dB, in average of the frequencies 0.5, 1, 2 and 4 kHz [8]. Some sources define a lower standard threshold at 15 dB for children [23]. A permanent HI greater than 35 dB is regarded as disabling by the WHO definition. The severity of the HI can be further classified into mild (20 to < 35 dB), moderate (35 to < 50 dB), moderately severe (50 to < 65 dB), severe (65 to < 80 dB), profound (80 to < 95 dB) and complete/deafness (≥ 95 dB) based on the measured threshold value [8]. The term deafness is sometimes used as a synonym for profound and complete HI but used with a capital "D" and in a cultural context, the term "Deaf" describes a societal group that uses sign language for communication [6]. HI can be further classified against several other domains than only thresholds (**Figure 2**).

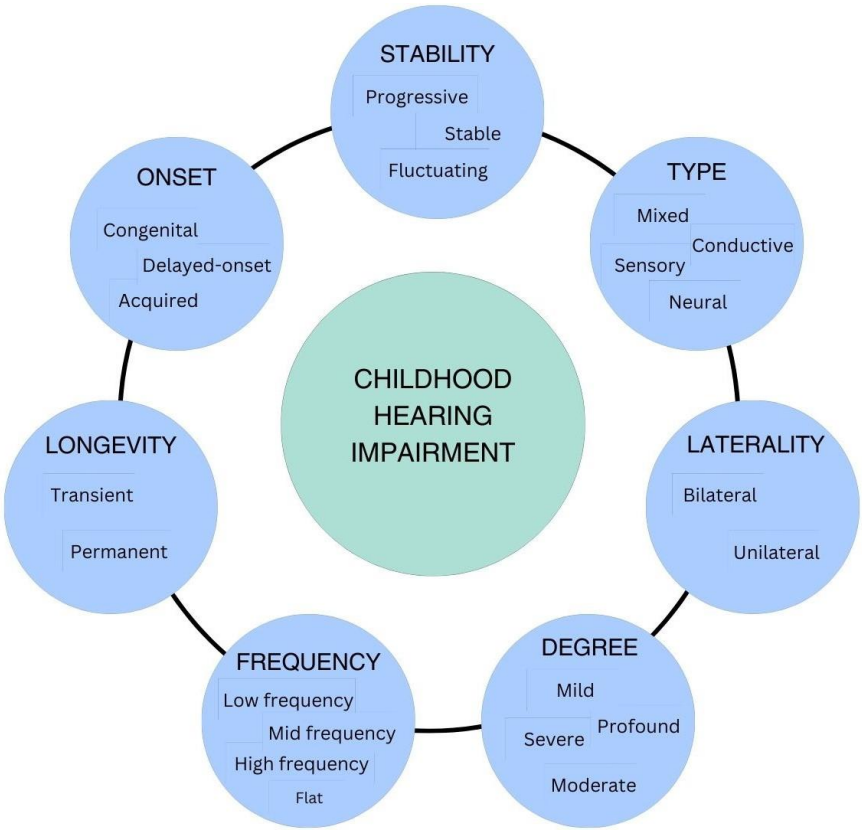


Figure 2. Domains of classification in childhood hearing impairment.

Reprinted by permission from [24]

ONSET: Based on time of the assumed onset, HI can be classified as ***congenital*** when identified in the neonatal period, ***delayed onset*** when recognized after the neonatal period but ascribed to perinatal etiologies, and ***acquired*** when both identified and ascribed to exposures that took place after the neonatal period [23].

STABILITY: When hearing thresholds are assessed over time, HI can be classified as ***stable***, ***fluctuating,*** or ***progressive*** [25].

TYPE: Based on the cause, HI can be classified as conductive, sensorineural or mixed [23]. ***Conductive HI*** is caused by pathology in the conductive auditory pathway. In children this includes both congenital ear malformations and chronic forms of otitis media, such as long-standing effusion [26, 27]. Most cases of otitis media-related HI are reversible, either spontaneous or by surgical treatment. ***Sensorineural HI (SNHI)*** is caused by pathology in the cochlea or the auditory nerve. SNHI is most commonly caused by damage to the hair cells (or their supporting structures) and can then also be assigned ***cochlear*** or ***sensory HI***. SNHI is more rarely caused by dysfunction in the auditory nerve, and then assigned as ***neural*** or ***retrocochlear HI*** [28]. The most common type of retrocochlear HI in children is auditory neuropathy that will be discussed separately. ***Mixed HI*** includes the combination of conductive and sensorineural HI. Lastly HI may be caused by dysfunction in the central auditory pathways, this will also be discussed separately.

Other domains of HI include whether it affects only one or both ears (**LATERALITY)**, whether the HI loss is transient or permanent (**LONGEVITY**), and the hearing thresholds in relation to different frequencies (**FREQUENCY**).

EXTENDED HIGH FREQUENCY (EHF) HI refers to reduced hearing thresholds in the extended higher frequencies > 8 kHz, which is above the conventional range covered in standard audiometric testing. Consequently EHF-HI may go undetected in standard hearing evaluations. HI in the EHF range can be an early indicator of noise and/or ototoxic damage [29], and may be associated with subclinical cochlear dysfunction in the standard frequency range [30]. EHF-HI is also associated with previous otitis media and tympanostomy tubes [31]. While children generally exhibit exceptionally sensitive hearing in the EHF region, age-induced decline in this range begins early in life [32], highlighting the importance of using age-specific reference thresholds when conducting EHF audiometry in children [4, 33]. The full functional aspect of human hearing in the EHF range 8-20 kHz is not fully understood. Beyond the direct

perception of high-pitched environmental sounds, EHF hearing is associated with speech-in-noise perception in children [30, 34].

AUDITORY NEUROPATHY SPECTRUM DISORDER (ANSD) OR AUDITORY NEUROPATHY (AN) is a type of neural HI, with dysfunction in the auditory nerve or in the synaptic structures of the inner hair cells. The prevalence of ANSD is uncertain, with reported estimates between 1-10 % of all pediatric SNHI [35]. ANSD is strongly associated with prematurity and neonatal morbidity but there are also other etiologies including genetic forms [36]. ANSD is distinguished from SNHI clinically by the presence of normal otoacoustic emissions but a pathologic brain stem response. The clinical presentation of ANSD is variable, ranging from mild to profound HI, with hearing thresholds that frequently fluctuate [35].

CENTRAL AUDITORY PROCESSING DISORDER (CAPD) is a condition with difficulties in processing and interpreting auditory information, despite normal peripheral hearing function, as indicated by standard hearing tests. Individuals with CAPD often struggle with discriminating and sequencing sounds, leading to challenges in understanding speech, especially in noisy environments [37]. Specialized test batteries have been developed to assess central auditory processing skills. However, the complexity of central auditory processing, which involves attention, working memory, cognition, and language skills, makes the underlying dysfunctions difficult to pinpoint. Consequently, there is no universally accepted definition or diagnostic criteria for CAPD. The condition has been approached in two main ways: one views CAPD as a broader dysfunction involving other higher-order functions, while the other considers it a more specific impairment related to auditory processing alone [38].

1.3.2 Prevalence of childhood hearing impairment

After the introduction of universal newborn hearing screening (UNHS) many reports on HI prevalence rates in children are available, but there is still a lack of a uniform methodology to define, measure and calculate prevalence rates of childhood HI [39]. Studies reporting permanent HI in the newborn population do mostly not distinguish between SNHI and conductive HI, but majority of permanent losses in this age group is of sensorineural etiology [40]. Globally, the prevalence estimates for HI in children and adolescents are reported to increase [41].

The prevalence of congenital HI in infants up to one year of age was in two recent systematic reviews reported to be around 1.1 per 1000 for bilateral HI, and 2.2 per 1000 when unilateral HI was included [42, 43]. Both studies reported significantly higher prevalence rates of HI in infants with a history of NICU admission, ranging from 6.9 to 15.8/1000. It is well documented that the prevalence of childhood HI increase with age. Fortnum observed around 80% rise in prevalence of permanent HI from 3 to 9 years of age in a British cohort [44], while Uhlen reported a 2-3-fold increase from infants to school children in a Swedish regional cohort [45]. This increase in HI cases is thought to represent late-onset or acquired HI but can also comprise congenital HI not identified by UNHS, and permanent conductive HI. Follow-up studies in childhood cohorts with HI do also report that deterioration in hearing is common [46].

1.3.3 Etiology of childhood sensorineural hearing impairment

HI in children is an etiologically diverse condition, arising from a variety of causes that include both environmental and genetic factors. The findings from etiological studies on childhood HI have changed over the past decades. In this section I will briefly present HI of genetic origin, HI after infections, HI secondary to middle ear disease and the concept ototoxicity. Recent studies also increasingly report neonatal complications, such as prematurity and asphyxia, as etiologies for HI [47], likely due to improved survival rates among these patients [48, 49]. Neonatal risk factors will be presented separately in 1.4.

1.3.3.1 Genetic hearing impairment

It has traditionally been assumed that around 50% of congenital SNHI in developed countries is genetic and the remaining cases equally divided between environmental and unknown causes [23, 50, 51]. More recent studies report proportions of 60-70% to be of genetic origin (**Figure 3**) [52–55] which is explained by advances in the field of medical genetics that have enabled the identification of many new genetic variants that are associated with HI [56].

In newborns genetic HI is non-syndromic in 70-90% of cases, while the remaining 10-30% present with a syndromic form that include a wide range of co-inherited anomalies [54]. More than 700 syndromes that include HI are described [6]. Mutations in the gene GJB2, that encodes for the protein Connexin, is the most common cause of non-syndromic genetic HI [6, 57], this

is also reported in Scandinavian cohorts [50, 58]. Genetic HI can also be caused by mutations in both nuclear and mitochondrial DNA. Some mitochondrial mutations are associated with increased risk for ototoxic damage and have therefore been of special clinical interest [59]. In ~80% of patients with non-syndromic HI the inheritance pattern is autosomal recessive, in ~20% autosomal dominant and in a small percentage X linked or mitochondrial (**Figure 3**).

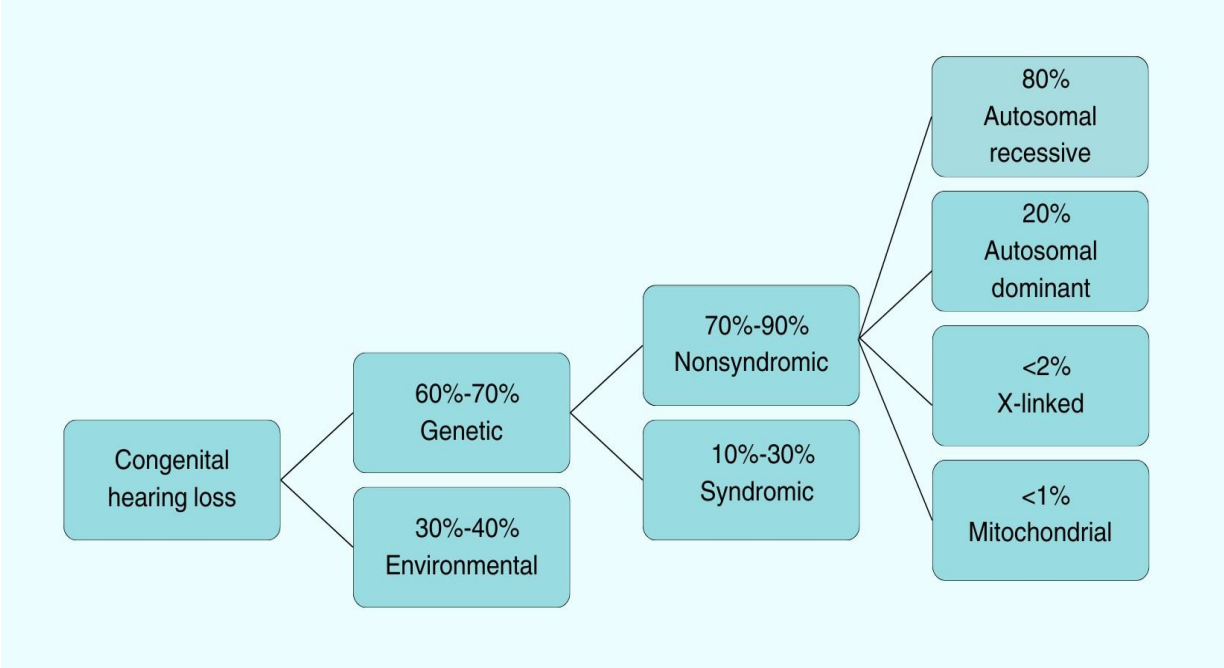


Figure 3. Etiology of congenital HI. Numbers for proportion estimates from Jonard et.al 2023 [55]

1.3.3.2 Hearing impairment secondary to infections

Several infections are causally linked to childhood SNHI [60, 61]. These can be classified as congenital, if the infection occurred during pregnancy, or acquired, if there was a postnatal infection.

Universal immunization programs have reduced many previously common infectious causes of SNHI, including viral (mumps, rubella, measles) and bacterial (Haemophilus influenzae and pneumococcal) diseases [61, 62]. For others, like HSV, the associations are insufficiently clarified and appear to be weak [63]. Toxoplasmosis is often listed as a causal agent for congenital SNHI but there is a paucity of studies on this association. A systematic review from 2009 reported no cases of SNHI in children who received antiparasitic treatment early in life

[64]. Historically, congenital syphilis has been recognized as a significant risk factor for SNHI, but the association is poorly defined in more recent studies, probably due to effective antibiotic therapy [65]. Recent studies have found a possible association intrauterine Zika virus infection and hearing impairment [66, 67].

Congenital cytomegalovirus (cCMV) is the most common infectious cause of SNHI in children in developed countries. Recent studies show that cCMV affects about 0.6-0.7% of newborns [68, 69] and is a significant contributor to various neurodevelopmental disabilities in childhood [68, 70, 71]. While most neonates with cCMV are asymptomatic, approximately 10% have clinical symptoms [72]. A recent systematic review reported that 30-70% of symptomatic neonates and 0-15% of asymptomatic ones experienced SNHI, late-onset cases occurred in both groups leading to a higher prevalence at follow-up later in childhood [71]. The auditory manifestations caused by cCMV are notably diverse; SNHI associated with cCMV range from mild to profound, may be uni- or bilateral, present at birth or develop later, and often progresses [70, 71, 73]. Antiviral therapy of cCMV, initiated in the first month of life, has shown some promise in improving hearing outcomes in children with cCMV, with some studies indicating significant benefits but also others showing limited or no improvement. The effectiveness also appears to depend on the timing and duration of treatment [74–78]. Targeted screening programs with cCMV testing for infants that do not pass their initial UNHS are recommended [79] and have been implemented in several countries, including Norway [80]. There is also ongoing debate about broader screening strategies, with testing of all pregnant women or universal screening for cCMV in all newborns [81, 82].

Bacterial meningitis is also well-documented risk factor for acquired SNHI, which is the most frequent neurological sequalae after bacterial meningitis. The prevalence rates of SNHI after meningitis range from 10 % to 32 % [83–87] and the severity of SNHI range from mild to profound [88, 89]. The risk of developing SNHI varies by bacterial agent, with the highest risk following pneumococcal meningitis and the lowest after meningococcal meningitis. Adjunctive dexamethasone therapy, started concomitantly with antibiotics, can reduce risk of SNHI and is best documented for infections with *Haemophilus influenzae* [90]. Age of onset does also affect risk for SNHI, with infants being particularly vulnerable to later SNHI. The pathophysiological mechanisms for post-meningitis SNHI include both damage to the inner ear from direct bacterial invasion and host inflammatory responses [85]. Viral meningitis can also lead to SNHI, but the risk is not well-established and appears to be lower [91].

1.3.4 Hearing impairment after middle ear disease

Middle ear disease primarily causes conductive HI but is also reported to elevate the risk for SNHI. Histopathological studies on temporal bones from patients with otitis media have clearly demonstrated cochlear pathology, particularly in the basal turn [92, 93]. This cochlear damage is likely caused by inflammatory cells and toxins [94–96]. Clinically, these findings align with studies showing that otitis media is associated with impaired hearing in the extended frequency range [31, 97, 98]. Otitis media has also been linked to SNHI within the conventional frequency range [99, 100] but a recent systematic review highlighted that conclusions are limited due to high risk for bias and suboptimal study designs [101].

1.3.5 Ototoxicity

Ototoxicity refers to harmful effects on the inner ear following exposure to toxic chemicals. Common ototoxic drugs in clinical use include platinum-based chemotherapeutic agents, salicylates, NSAIDs, loop diuretics, and aminoglycosides. Ototoxic effects can affect both the vestibular and cochlear system. The type and severity of symptoms can vary based on drug type, dosage, and individual factors such as genetic predisposition and synergistic effects from other risk factors like several ototoxic drugs administrated together, noise exposure, and systemic inflammatory responses [102–105].

1.3.5.1 Ototoxic induced hearing impairment

Ototoxic-induced HI typically presents as symmetrical and irreversible, initially affecting the highest frequencies [106–108]. EHF audiometry covering the frequencies > 8 kHz is therefore a sensitive test for detecting ototoxic HI and is recommended for monitoring [109, 110].

1.4 Neonatal Risk factors for hearing impairment

1.4.1 Neonatal period – general aspects and risk of hearing impairment

The neonatal period is defined as the first 4 weeks after birth and represents a vulnerable time period for all children. Neonatal health is also closely related to factors in the perinatal period (**Figure 4**). Perinatal and neonatal disease that encompass hemodynamic changes, hypoxia, infections, and ototoxic medications, can all lead to neurological complications, including SNHI [111]. Many of these factors can co-exist and appear to the represent cumulative risk

[112] but how they possibly interact through synergistic effects, is poorly clarified. There are few studies evaluating risk for HI in NICU-infants with access to more detailed data on clinical variables and perinatal risk factors.

"Admission to NICU", is in many studies and guidelines used as an individual variable, to measure risk for HI [113] and illustrates these challenges. As a group it is well documented that infants admitted to NICU have a significantly higher and up to 15-fold increased risk for HI [42, 43]. A history of NICU admission is also reported to be associated with greater risk for late-onset HI [114]. But the "NICU population" is large, very heterogenous and includes both term infants admitted for short observation after birth and infants with life-threatening illness receiving advanced intensive treatment over long time periods. To provide the best risk assessment for SNHI as a long-term outcome, and to identify those in need for closer surveillance programs, we need more knowledge on the effect of the individual neonatal risk factors and on how they interact.

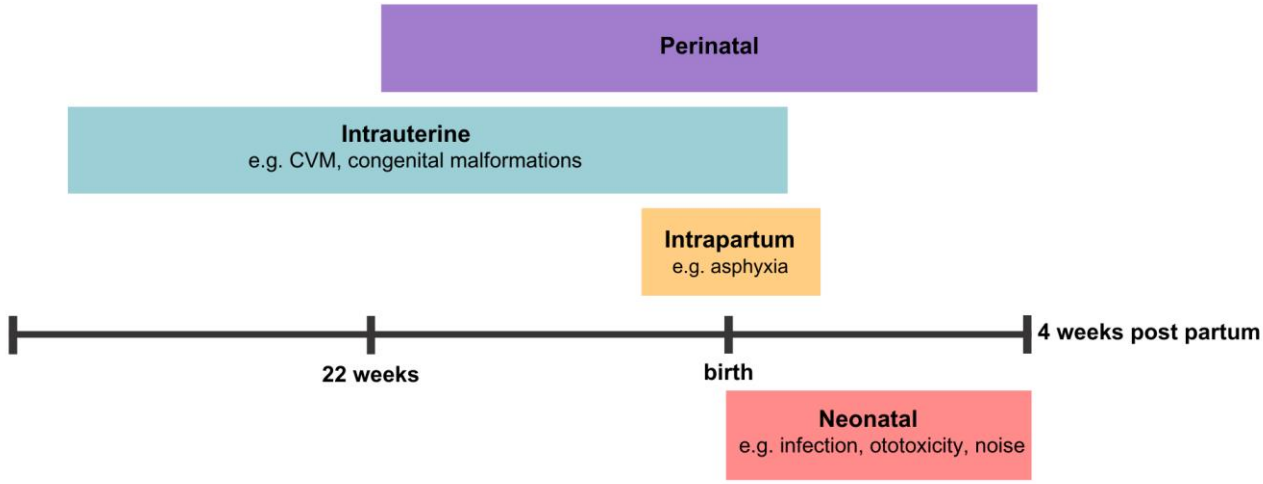


Figure 4. Risk factors for hearing impairment from early in the pregnancy until the end of the neonatal period.

1.4.2 Aminoglycosides - ototoxicity and mitochondrial mutations

Aminoglycosides are a class of antibiotics effective against Gram-negative bacteria, often used in combination with beta-lactam antibiotics for empiric therapy of sepsis in both adults, children and neonates [115]. Aminoglycosides are among the most commonly used drugs in the NICU [116]. Despite their benefits, such as low antimicrobial resistance and cost-effectiveness, aminoglycosides are known for their ototoxic potential [105, 117]. There has been particular concern about ototoxic side effects in neonates due to the wide use of gentamicin in the NICUs [118] and general vulnerability of HI in this population.

Aminoglycosides are bactericidal antibiotics that inhibit bacterial protein synthesis by binding to ribosomes and disrupting RNA attachment. Their effectiveness increases with higher drug concentrations inside the bacterial cell, making their action concentration-dependent [119, 120]. Extended-interval dosing of aminoglycosides, which involves administering larger doses less frequently, is recommended for neonates in current guidelines [121]. These dosing regimens provide several advantages, such as enhanced bactericidal effects from higher peak concentrations, increased post-antibiotic effects, reduced bacterial resistance, and decreased toxicity risk due to extended periods with sub-toxic drug levels [122, 123]. However, there is still uncertainty about the optimal dosing regimen, especially concerning potential toxic effects [124].

Current evidence indicates that neonates have a low risk for HI after gentamicin treatment, but due to lack of studies with robust data, the understanding of gentamicin's ototoxic effects in neonates is limited and less conclusive than in older children [108, 125, 126].

The ototoxic effects of aminoglycosides were first recognized with the clinical introduction of streptomycin in the 1940s [127]. The different aminoglycosides are reported to vary in their ototoxic profile: Gentamicin and tobramycin are known to be more vestibulotoxic, affecting balance, whereas amikacin, neomycin, and kanamycin are more cochleotoxic, impacting hearing [105, 128]. Systemically administered aminoglycosides cross the blood-labyrinth barrier and enters the endolymph where it is taken up by hair cells [127]. Inside the hair cell, damage and cell death can be initiated through several different mechanisms [129]. This damaging process typically starts in the basal high frequency region of cochlea and can then progress with continued dosing [130]. The gentamicin formulation used for therapy is a mixture of five main C-subtypes, and recent research shows these subtypes differ in ototoxic potential

due to their distinct affinities for hair cell channels. Modifying the subtype composition could therefore potentially reduce ototoxic effects while preserving antibacterial efficacy [131].

Several variants on mitochondrial genes have been reported to increase the risk for ototoxic SNHI after exposure to aminoglycosides [59]. The MT-RNR1 gene, particularly the m.1555A>G mutation, is most commonly associated with this increased risk [132]. The m.1555A>G mutation is also associated with SNHI without aminoglycoside exposure [133]. The prevalence of m.1555A>G vary across ethnic populations and is reported to be 0.2-0.3 % in studies from Europe [134, 135]. Despite the well-documented risk, both the penetrance and expressivity of this mutation vary [136, 137].

1.4.3 Preterm birth and associated neurological complications

Preterm birth is a leading cause for neonatal mortality [138], and a major risk factor for neurodevelopmental disabilities [139], including sensory impairments in childhood [140]. Despite advances in peri- and neonatal care, and improved survival rates in preterm infants [48], the burden of long- term disabilities have remained high [141, 142].

Preterm birth is defined as delivery before 37 weeks gestational age (GA) and is further categorized into moderate to late preterm (GA 32-36 weeks) very preterm (GA 28-31 weeks) and extremely preterm (GA 22-27 weeks) birth [143]. The rates of mortality, neonatal morbidity and long-term neurodevelopmental disabilities increase markedly with decreasing GA [144, 145]. This trend is also observed for SNHI [146, 147], although outcomes are influenced by various other factors. The risk for SNHI is believed to be multifactorial and can be etiologically linked to both immaturity of the auditory system [148] and presence of other disease and treatments associated with preterm birth [112, 149].

Birth weight (BW) is closely correlated with GA, yet intrauterine growth restriction can result in weights below expected levels for a given GA, a condition known as small for gestational age (SGA). SGA independently increases the risk of various adverse long-term outcomes, including neurodevelopmental and sensory impairments [150, 151]

Most preterm births occur spontaneously while some cases are due to induced delivery because of maternal, fetal or placental complications, with pre-eclampsia being the most common reason [152]. The etiological mechanisms behind preterm birth are still poorly understood but

numerous risk factors have been identified, including infections, multiple pregnancies, and maternal health issues [153]. Foetal conditions such as genetic factors affecting growth, immunity, and inflammation may also affect the risk, and even the outcomes, of preterm birth [154, 155].

Prematurity is also associated with various neurological complications. Intracranial haemorrhage (ICH), linked to immature and fragile vessels in the germinal matrix, is a common complication in extremely preterm infants and the incidence increases with decreasing GA [156]. Based on the severity and location of the bleeding, ICH can be classified from grade I-IV according to the Papile grading system [157]. The outcomes after ICH vary widely, ranging from minor to severe, and include diverse neurological impairments including increased risk for HI [158]. Another significant brain injury, cystic periventricular leukomalacia, involves necrosis around the ventricles and is often linked to motor disabilities like cerebral palsy, and is also reported with association to HI [159].

1.4.4 Perinatal asphyxia and neonatal encephalopathy

Perinatal asphyxia is a condition where the neonate experience lack of oxygen due to hypoxic or ischemic events occurring close to or during birth (peri- or intrapartum) [160, 161]. Many different complications related to pregnancy and birth can cause perinatal asphyxia, including e.g. ruptured uterus, placental abruption, obstructed labour and umbilical cord prolapse. In neonates, impaired gas exchange with oxygen deprivation can result in multi-organ failure, with the brain being the primary organ affected, leading to hypoxic-ischemic encephalopathy (HIE). Often, HIE is accompanied by hypoxic-ischemic damage to other critical organs such as the heart, kidneys, lungs, and liver.

Neonatal encephalopathy (NE) is an umbrella term for central nervous system dysfunction in term and near-term infants, that can arise from various conditions [162]. Thus hypoxic-ischemic encephalopathy (HIE) does not explain all instances of neonatal encephalopathy. The term NE is preferred because it covers the clinical syndrome without implying a specific cause or underlying brain injury mechanism. The diagnosis of HIE should only be used when perinatal asphyxia is considered the primary cause of NE. Central parameters for diagnosing asphyxia include a poor clinical condition, often measured by Apgar score, combined with cord blood metabolic acidosis and postnatal neurological abnormalities, but a definitive set of clinical signs

or biomarkers that can confirm peri- or intrapartum hypoxic ischemia is lacking [163, 164]. HIE is a leading cause of neonatal brain injury causing mortality and neurodevelopmental sequala including motor impairments like cerebral palsy, intellectual disability, and sensory impairments. The highest incidence of HIE is found in low- and middle-income countries. The pattern of brain injury in HIE is related to severity, duration, and pattern of hypoxia. Neurons appear to be more vulnerable to injury than glial cells. The pattern of injury affects cell groups with high metabolic activity first, rather than following a macrovascular pattern, this is referred to as "pattern of selective neuronal cell death".

Therapeutic hypothermia (TH) is well documented to reduces the risk of death and disability in infants with moderate to severe HIE and is today a well-established treatment in high-income countries [49, 165]. TH should be initiated as soon as possible and no longer than 6 hours after birth, and it is common clinical practice to use selection criteria from the largest clinical trials on TH to select babies for TH [166–168].

Increased risk for SNHI is reported after isolated low Apgar scores, and after asphyxia by various definitions [169–172]. However, the risk for SNHI appears to be best described in TH-populations with reported prevalence rates of SNHI as high as 10% [173]. A recent systematic review and meta-analysis reported a 5% pooled prevalence of SNHI among 4868 cooled infants from 19 studies [174]. A possible protective effect from TH on SNHI is not yet documented, but data and reports on hearing outcomes in cooled infants are scarce compared to other neurodevelopmental outcomes [49, 165, 175].

1.4.5 Hyperbilirubinemia

Hyperbilirubinemia is common in neonates, most often mild and self-limiting, but can cause bilirubin-induced neurologic damage (BIND) at high levels. When bilirubin levels increase, a higher fraction remains unbound to albumin, this unbound bilirubin can pass the blood-brain barrier and has neurotoxic potential [176]. The auditory pathway is particularly susceptible to hyperbilirubinemia [176–178]. The retrocochlear structures, with the cochlear nerve and the auditory nuclei in the brain stem, appear to be more vulnerable for BIND than cochlear structures [177]. BIND is associated with pathological brain stem responses and can clinically manifest as ANSD in both transient and permanent forms [36, 179]. Preterm neonates, with their immature metabolism and more permeable blood-brain barrier, are at a higher risk for

developing hyperbilirubinemia and are more susceptible to BIND, experiencing adverse effects at lower total bilirubin levels than full-term neonates. [180].

1.4.6 Respiratory diseases and respiratory support

Respiratory complications are common in many neonatal morbidities and can be independently associated with an increased risk of various neurodevelopmental impairments [181, 182] . Premature infants often experience respiratory distress syndrome (RDS) due to immature lungs and surfactant deficiency, with the incidence rising as gestational age decreases. RDS can necessitate prolonged mechanical ventilation and medical treatment [183], increasing the risk of bronchopulmonary dysplasia (BPD)- a chronic lung condition defined by the need for oxygen or respiratory support at 36 weeks postmenstrual age [184]. The administration of antenatal steroids (in pregnancies below 34 weeks gestation) has been shown to markedly reduce respiratory complications and mortality among preterm neonates [185]. Additionally, this treatment is likely to improve neurodevelopmental outcomes [141] and is in a recent systematic review also reported to reduce the risk for HI [186].

Respiratory complications are common among neonates treated with gentamicin; this heterogeneous group includes various underlying morbidities and often comprises preterm infants. Additionally, neonatal sepsis, the target condition for gentamicin treatment, can itself involve respiratory complications and necessitate respiratory support [187]. This complicates the assessment of risk factors for HI; is it due to ototoxic effects of gentamicin or due to invasive respiratory support? Infants suffering from HIE do also have high risk for respiratory complications due to various factors, including meconium aspiration syndrome, pulmonary hypertension and direct hypoxic brain stem injury affecting central respiratory regulation and drive [188].

In summary, respiratory complications are closely associated with all the main exposures investigated in this thesis, preterm birth, gentamicin treatment, and perinatal asphyxia. Prolonged mechanical ventilation is in many studies reported to increase the risk for both early- and late-onset SNHI, but whether this represent an independent risk factor for SNHI is not clarified [170, 189, 190].

1.4.7 Auditive brain stem responses in premature and sick infants

The last trimester of pregnancy is a critical period for maturation of the auditory system, characterized by myelination of the auditory nerve, resulting in faster and more synchronized signal transmission [17]. In preterm infants, entire or parts of this process, takes place in an extrauterine environment and is associated with delayed or disrupted maturation.

A meta-analysis concluded that shorter GA is associated with delayed auditory conduction times in normal hearing infants [148]. Results from a study comparing results from automated auditory brainstem response (AABR) tests in normal hearing infants born at after 32 weeks of postmenstrual age with infants born at lower GA, suggested that the extrauterine auditory system maturation of infants born very and extremely preterm is delayed [191]. This delayed maturation may explain the observed instability in hearing function in preterm infants, with possibility for both improvement and deterioration after the neonatal period [192–196] and why prematurity is strongly associated with ANSD [36]. Delayed auditory brainstem responses may also indicate broader maturation abnormalities and potentially predict later developmental issues [197].

It also reported that asphyxia [198, 199] , other neonatal morbidity [148, 191], particularly hyperbilirubinemia [177, 180] can affect and delay auditory brain stem responses during, and beyond the neonatal period.

1.5 Diagnostic Hearing Tests in infants and children

Sound is vibration in a medium, usually air. Sound has intensity (loudness), frequency (pitch), periodicity, and duration. The loudness of sound is measured in decibels (dB), a logarithmic scale and frequency is measured in hertz (Hz). The human ear perceives sounds in the frequency range between 0.02 to 20 kHz, with highest sensitivity in the range between 0.5 and 4 kHz, covering most speech sounds.

Audiologic testing quantitatively evaluates hearing. Depending on the tests, the resulting audiometric profile can indicate both extent and pattern of HI and identify the type and localization of auditory dysfunction. Measurements of hearing are displayed in **Table 1** and can be classified into [200]:

- Objective hearing tests; electrophysiological or electroacoustic methods
- Subjective hearing tests; psychoacoustic methods using audiometry

Table 1. Classification of hearing tests

Objective hearing tests	**Subjective hearing tests**
Auditory brain stem response (ABR) Auditory steady-state responses (ASSR) Otoacoustic emissions (OAE) • Transient-evoked (TEOAE) • Distortion-product (DPOAE)	Audiometry Pure tone audiometry Visual reinforcement audiometry Play audiometry

Objective hearing tests, such as otoacoustic emissions (OAE) and brainstem responses, do not require active cooperation from the test subject, making them crucial for assessing hearing in infants and younger children. These tests measure activity at specific sites along the auditory pathway, indirectly estimating hearing thresholds. In contrast, subjective hearing tests that include various forms of audiometry are based on active responses from the test subject, directly reflecting hearing on a cortical and conscious level.

1.5.1 Objective hearing tests

1.5.1.1 Otoacoustic emissions

Otoacoustic emissions (OAE), first described by David Kemp in 1978, are acoustic energies produced by hair cells that can be recorded with a microphone in the ear canal. OAEs can arise spontaneous or be induced by sound stimuli [201, 202]. An OAE test is quick and easy to perform, has high sensitivity and specificity, and suitable for newborn hearing screening. With settings for screening, the OAE device can produce either a pass or failed result, and where a passed response typically indicates a hearing threshold at 25-30 dB or better. The most common types of OAE in clinical use are transient-evoked OAEs (TEOAEs) and distortion-product OAEs (DPOAEs).

TEOAEs are broadband emissions, arising from a wide portion of cochlea in response to click stimuli. The emissions are delivered with different latencies and can be deconstructed into frequency bands after recoding [202]. DPOAEs, arise in response to tones that give rise to so called distortions. The DPOAE test is more sensitive to high-frequency hearing impairment, with better potential to detect early ototoxic hearing impairment [203].

Mild HI is difficult to detect with OAE technology. Another limitation of acoustic emissions is that they are affected by status of the ear canal and the middle ear [202]. For instance, conditions commonly seen in infant and childhood populations like vernix in the ear canal or fluid in the middle ear can reduce or prevent emission measurement, resulting in false positive TEOAE tests despite a normal cochlea [204]. Lastly, OAE only reflects the status in cochlea and will not be able to detect retrocochlear pathology.

1.5.1.2 Auditory brain stem responses

The auditory brain stem response (ABR) is an electrophysiological technique that detects auditory evoked potentials in the brainstem. It can provide estimates of hearing thresholds and is an important method for diagnosing SNHI in infants younger than 6 months [113], it can also be used to assess the auditory pathway to identify quality of neural response and pathological lesions.

ABR testing exposes the test subject to short and transient sound stimuli at varying levels (dB) generating evoked potentials measured by using surface electrodes on the scalp. The full ABR in a person with normal hearing typically show seven peaks, labelled sequentially from I to VII (**Figure 5**). However, typically only waves I, III, and V are used clinically. The primary measurements from an ABR are the absolute wave latencies, amplitudes, and interwave intervals between waves I to III ("peripheral component; nerve conduction"), between waves III to V ("central component; brain stem conduction"), and between waves I to V ("total latency"). The final ABR result is the averaged responses to several thousand repetitions of a stimulus. ABR testing can be done with different types of sound stimuli—clicks, tone bursts, and chirps—that have different test qualities and target different frequency ranges [200].

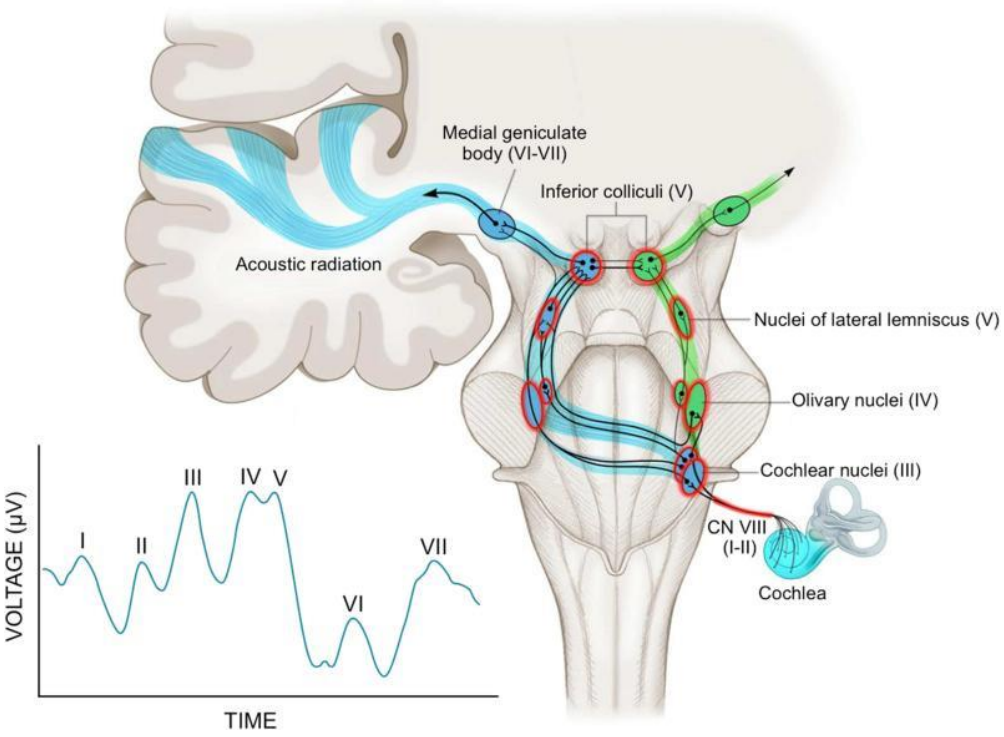


Figure 5. Brain stem evoked auditory potentials. Illustration from the "Ear Anatomy" series, by Robert Jackler and Christine Gralapp. Reprinted with permission.

Brain stem responses can also be automatically recorded in response to a preset hearing threshold, typically at 35 or 45 dB, resulting in either a 'passed' or 'non-passed' outcome. This method, known as automated brain stem audiometry (AABR), is often employed for universal hearing screening in selected groups and as follow-up after a non-passed OAE screening.

1.5.1.3 Auditory steady-state responses

The auditory steady-state responses (ASSRs) are also auditory evoked potentials but arise in response to regularly repeating stimuli. ASSR is routinely used as a supplement to ABR to estimate hearing thresholds in a broader frequency range, and it facilitates hearing device fittings, especially in infants whose hearing rehabilitation should be initiated as early as possible for reasons of speech development [200].

1.5.2 Subjective hearing tests

Pure tone audiometry is regarded the gold standard for measuring hearing thresholds. The pure tone hearing threshold is defined as the lowest level of sound perception (dB) at a given frequency (Hz). Conventional pure tone audiometry measures hearing thresholds in in the frequency range between 0.25 kHz (or 0.125 kHz) and 8 kHz [200]**. Extended high frequency (EHF) audiometry** measures hearing thresholds in the frequency range above 8 kHz and up to 20 kHz. Audiometry is conducted in a sound-insulated room compliant with ISO standards to ensure accuracy. **Figure 6** displays a normal audiogram for both the standard and EHF frequencies. In pure tone audiometry the tones can be presented by both air and bone conduction. This method makes is possible to determine if the anatomical site for reduced sound transmission is in the ear canal/middle ear (conductive HI) or in the cochlea or auditory nerve (SNHI).

There are two common dB scales in audiology: Sound Pressure Level (SPL) and Hearing Level (HL), both representing logarithmic ratios. dB SPL measures absolute sound pressure without adjusting for frequency sensitivity, while dB HL, commonly used in clinical settings, is referenced against the zero dB HL line—a standardized threshold adjusted for the varying sensitivity of human hearing across different frequencies [205].

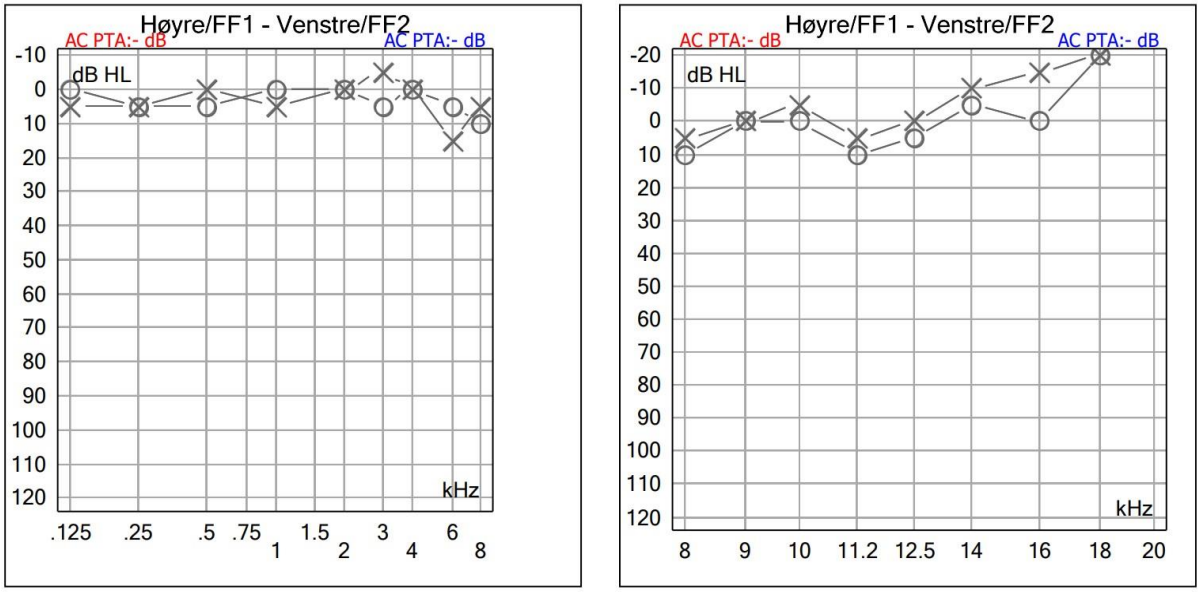


Figure 6. Air conducted audiogram with normal hearing thresholds for both standard (1.25-8 kHz) and EHF (9-18 kHz) frequencies in an 8-year-old girl. Right ear displayed with circles and left ear with crosses. Private recording.

For children too young to participate in conventional audiometry, age adjusted behavioural hearing tests constitute the gold standard for estimating hearing thresholds [113]. **Visual reinforcement audiometry** is suited for infants from the age of 4-6 months and uses a conditioned response. When the infant turns to look toward the sound source, a visual reward is given to reinforce the behaviour [206]. **Play audiometry** adapts the audiometry into a game to engage children, replacing button presses with playful actions like placing a block in a bucket. Play audiometry is appropriate for children with developmental age ranging from 2 to 5 years [207].

1.6 The impact of early detection and auditory intervention

Research indicates a critical time-period for auditory stimulation in children born with deafness or HI, and the ability to perceive and process sound is compromised if the brain does not receive auditory stimulation during the first 3-4 years of life [208]. Within this critical timeframe, earlier intervention significantly improves outcomes, with benefits diminishing as the intervention is delayed [209]. This knowledge correlates with results from numerous clinical studies providing solid evidence on that early auditory intervention in hearing impaired children is associated with significantly better outcomes for language and general development [210–212].

A Swedish study with children who received cochlear implants (CI) between 2002-2013 found that those implanted before 9 months exhibited age-appropriate language skills by age four and performed better than children implanted after 12 months. [213]. A recent systematic review reported overall improved auditory outcomes in children implanted a CI ≤ 12 months of age [214]. An American study, with a study cohort recruited from CI centers across the US, also reported best long-term outcomes in adolescence for those implanted before 18 months of age [215].

Early identification to provide early intervention is therefore critical in paediatric audiology and the rationale for UNHS programs. The so called 1-3-6 strategy was introduced by the Joint Committee of Infant hearing-JCHI [216, 217] and is now a widely accepted recommendation included in many national guidelines. The strategy recommends newborn hearing screening to be completed by the age of 1 month, a HI diagnosis clarified by the age of 3 months and intervention with hearing devices implemented before the age of 6 months.

1.6.1 Universal newborn hearing screening

There is solid evidence that UNHS lowers both the mean age of being diagnosed with HI and the mean age for fitting of hearing devices [218, 219]. Thus, children identified in UNHS programs have better outcomes for both language [218] and general development [219, 220]. A clear cost-benefit effect of UNHS is also demonstrated in several studies [221].

Both WHO [8] and JCHI [113], along with several national health authorities [222] have published recommendations for UNHS. Today UNHS programs are established in most high-income countries [223] and in Norway since 2008 [224, 225]. Specific guidelines for the

Norwegian UNHS program were published in 2016 [80]. The coverage and the sensitivity of the Norwegian UNHS program remain to be evaluated.

The main tests used in UNHS, OAE and AABR, both have high sensitivity, specificity, and high negative and positive predictive values, whether applied independently or together [42]. Unlike OAE, AABR screening can detect retrocochlear pathology like AN [226, 227] and is therefore often recommended as method for UNHS in populations at risk for AN. The Norwegian protocol, based on guidelines from JCHI, recommends OAE screening for healthy infants and AABR for high-risk infants, defined as those admitted to a NICU for more than 48 hours [80, 216].

1.6.2 Hearing detection programs beyond newborn screening.

A significant amount of childhood HI will not be detected with UNHS [228, 229]. This can be caused by loss to follow up after screening, that vary in extent across programs [230]. Other cases not detected by UNHS can include mild HI, that mostly pass the screening test and later onset HI. There is therefore consensus for surveillance of HI in the childhood population beyond the newborn period [231, 232] but the best strategy to achieve early detection is still debated.

The JCHI guidelines [113, 216] recommend targeted surveillance for children based on risk factors associated with HI. Another, or additional, strategy is screening for HI in the general childhood population [232]. In Norway all children are offered regular consultations at public health care centers for a monitoring of general health and development [233]. Hearing assessments are part of these consultations, and at age 5, children undergo pure tone audiometry conducted by a nurse at the health care center. In addition to this, it is recommended that defined high risk groups are offered hearing tests in audiological clinics [234].

1.7 Hearing devices

Modern hearing devices use digital technology to create sound signals that can aid the hearing-impaired user to hear in different listening environment. There are two main categories of hearing devices: hearing aids (HA) and cochlear implants (CI).

Hearing aids (HAs) work by amplifying acoustic sound. The sound is detected in a microphone, amplified in distinct frequency bands by a transducer, and subsequently channeled into the ear via the ear canal [205]. Bone anchored hearing aids are anchored in the temporal bone and transmit sound directly to the cochlea, bypassing the ear canal and middle ear [235]. These devices can be useful for children with diseases, malformations, or absence (atresia) of the ear canal or middle ear.

In cases of severe to profound HI where peripheral sound amplification is not sufficient for auditory perception, the alternative is CI. This is a surgically implanted device that stimulates the auditory nerve directly, irrespective of cochlear function [236]. The surgical procedure of a CI involves embedding an internal component and positioning an electrode within the cochlea to directly activate the auditory nerve [237]. The external portion of the CI device captures environmental sounds, converts them into digital signals, and sends them to the internal component, which then triggers the electrodes to stimulate the auditory nerve [236]. The sound from a CI is a synthesized digital signal with a narrower range of frequency resolution and consequently necessitates more extensive auditory training.

To benefit from intervention with both HA and CI, it is necessary that children use their devices correctly and consistently [238]. Modern devices allow monitoring of usage time and is important for the follow-up process. Higher daily use is associated with improved language outcomes [239]. Reduced compliance is still a challenge for many hearing-impaired children and can be a result of limited knowledge of developmental benefits, technical challenges, and social stigma [240–242].

The acoustic sound produced by traditional HAs offers a more realistic auditory experience compared to the digital sound signals from CIs. Still, no hearing device can fully replicate the experience of normal hearing. Another significant limitation of wearing HAs is the reduced ability to overhear conversations unintentionally, which provides linguistic context and constitutes a substantial portion of daily language exposure [243]. Auditory training is therefore essential to fully benefit from hearing devices, with more extensive training required after receiving a CI.

1.8 Hearing habilitation

There have been substantial changes in diagnostics and habilitation of pediatric HI in the past 30 years [23, 244]. Advances in the HA technology, and particularly the introduction of the CI technology in the 1990ies, have enabled a new generation of children with severe to profound HI, to learn and use spoken language [245, 246]. Knowledge about the prognostic gain of early intervention, and the introduction of UNHS, have led to both earlier and more extensive use of hearing devices and auditory training.

Historically sign language was the only fully available language for people with severe and profound HI. Today, most parents can choose between spoken language, sign language, or a bilingual combination of both for their hearing-impaired child. The vast majority, with around 95%, of hearing-impaired children have parents with normal hearing [247]. The future of sign language, and the best way to use sign language in combination with auditory training is still a matter of a complex debate [248]. There is also lack of research on how the combination of sign and spoken language affect the outcome of spoken language [249] but more recent research [250] do not find that the addition of sign language improves the outcome of spoken language.

Habilitation of HI is a specialized and multi-professional function that include otorhinolaryngologists, audiologists, technicians/engineers and speech and language therapist.

2 Aims of the thesis

The overall aim of this thesis is to study and better clarify the association between morbidities and therapies in the neonatal period and their associated risks of later childhood sensorineural hearing impairment (SNHI).

In the thesis I focus on three specific suggested risk factors for SNHI; gentamicin therapy, perinatal asphyxia and neonatal encephalopathy, and preterm birth.

The aims of the three studies are:

Paper I

To assess long-term safety of a high-dose neonatal gentamicin regimen, with detailed hearing assessment of schoolchildren exposed to this antibiotic regimen in the neonatal period.

Paper II

To identify the association between perinatal asphyxia, neonatal encephalopathy, other neonatal morbidities, and being diagnosed with sensorineural hearing impairment, recorded during minimum 5-year observation period after birth.

Paper III

To identify the association between preterm birth, other neonatal morbidities, and being diagnosed with sensorineural hearing impairment, recorded during minimum 5-year observation period after birth.

3 Materials and Methods

This thesis is based on three papers that employed different methodologies, data sources, and analytical approaches. **Paper I** was a clinical study while **Paper II** and **Paper III** were registry studies. **Table 2** provides a summary of the methodological framework for each paper.

3.1 Setting and data sources

3.1.1 Paper I

For **Paper I** the data source was a clinical cohort from the NICU at the University Hospital in Northern Norway in Tromsø. This NICU is the only neonatal unit offering care for infants born before 32 weeks' gestation, and all other newborn infants in need of mechanical ventilation or intensive care, in the two northern-most counties in Norway. The original cohort included 440 children that had been treated with an extended-interval high-dose gentamicin regimen as neonates in the time-period 2004-2012. A previous study of this cohort had evaluated the safety of this dosing regimen and reported that the majority of trough plasma concentrations (TPC) were in the normal range, with low numbers of prescription errors and no indication of early ototoxicity, based on evaluation of TEOAE results at discharge [251].

3.1.2 Paper II and III

For **Paper II** and **Paper III**, we gathered and linked individual-level data for the study subjects from five national health and social registries in Norway. The Medical Birth Registry of Norway (MBRN) provides prospectively collected data on pregnancy, delivery, maternal and neonatal health, with a high rate of coverage. The Norwegian Patient Registry (NPR), initiated in 2008, holds diagnostic and procedural information (using the International Classification of Diseases, 10th Revision - ICD-10) submitted by both public and private healthcare providers. Reimbursement for patient care is directly linked to the reported diagnostic and procedural codes, assuring a high completeness of data. The Norwegian National Insurance Scheme (NIS) is the social security service in Norway and offers financial support for illness-related expenses, irrespective of individual income or wealth. All individuals eligible for financial support due to a specific health condition, including hearing impairment, are registered in NIS with the corresponding ICD-10 code. Norwegian Cause of Death Registry provides information on the time and cause of death, while Statistics Norway (SSB) provides data on educational level and immigration status of parents.

Table 2. Methodological outline of thesis

	Paper I	**Paper II**	**Paper III**
Title of paper	"Hearing in Schoolchildren After Neonatal Exposure to a High-Dose Gentamicin Regimen"	"Hearing impairment after asphyxia and neonatal encephalopathy: a Norwegian population-based study"	"Sensorineural hearing impairment among preterm children - a Norwegian population-based study"
Published	Pediatrics 2020	Eur J Pediatr 2024	Arch Dis Child Fetal Neonatal Ed 2024
Design	Clinical cohort study	National registry study	National registry study
Setting	Children treated with gentamicin as neonates, recruited from a NICU unit at a regional hospital. N= 226	National birth cohort of term born infants 1999-2014 N= 866 232	National birth cohort of preterm infants 1999-2014 N= 60 023
Time period (for exposure)	2004-2012	1999-2014	1999-2014
Primary exposure	Treatment with gentamicin, in a high-dose regimen, in the neonatal period	Perinatal asphyxia and neonatal encephalopathy	Preterm birth in 3 categories; extreme-, very- and moderate-late preterm infants

Data used to measure primary exposure	Clinical data from NICU:
	• Data on gentamicin
	  • Cumulative dose
	  • Trough plasma concentration
	• Other morbidities
	• Other therapies
		Registry data:
		• Apgar scores
		• NICU admission
		• Neonatal seizures
		• Therapeutic hypothermia
			Registry data:
			• Gestational age
			• Other morbidities
			• Other therapies

Outcome	Hearing levels in school age measured with conventional and extended high frequency audiometry	Clinical diagnosis of sensorineural hearing impairment	Clinical diagnosis of sensorineural hearing impairment
Data used to measure outcome	Average hearing level in the midfrequencies (0.5–4 kHz) and the EHFs (9–16 kHz).	ICD-10 codes from the national patient registry and the national insurance scheme	ICD-10 codes from the national patient registry and the national insurance scheme
Age at follow up for measurement of outcome	6-14 years	5-20 years	5-20 years
Statistical method	Linear regression models	Logistic regression models	Binomial regression models
Ethical approval	Regional Ethical Committee for medical and health research ethics	Regional Ethical Committee for medical and health research ethics	Regional Ethical Committee for medical and health research ethics
Reporting guideline and trial registration	STROBE ClinicalTrials.gov registration	STROBE	STROBE

3.2 Study populations

3.2.1 Paper I

From the original NICU cohort we invited 357 children for a detailed hearing assessment at 6-14 years of age, of whom parents/care givers of 226 children responded and agreed to participate, constituting the study population for **Paper I**. All parents completed a questionnaire (attached in Appendix) with questions about episodes of middle-ear infections, any treatment with tympanostomy tubes, and any episodes of intravenous antibiotic treatment beyond the newborn period.

We also recruited 33 healthy children in the same age group from local (public) schools, who had not been admitted to NICU, never had been exposed to aminoglycosides, and had no history of hearing problems or tympanostomy tubes.

3.2.2 Paper II and III

The study populations for **Paper II** and **Paper III** constituted all live-born infants in Norway, recorded in the MBRN, in the 16-year time-period from January 1999 to December 2014. However, we excluded children who died during the first two years of life due to insufficient follow-up time for a HI diagnosis.

Paper II (assessing the influence of asphyxia/neonatal encephalopathy on SNHI) included all infants born ≥ 36 completed weeks gestation, thus the age group that according to national guidelines can be eligible for TH [252]. We excluded most preterm infants (except those born in 36 weeks gestation) to remove any influence of prematurity. For children with missing or obviously incorrect registered data for GA, we included those with BW ≥ 3000 grams and pragmatically assigned them a GA of 37 weeks.

Paper III (assessing the influence of preterm birth on SNHI) included all preterm infants with a GA from 22 through 36 weeks. We excluded children with a BW Z-score for GA outside ±3SD, as many of these contained implausible values for BW, most likely representing false values from data entry errors. GA was determined by foetal ultrasound data, routinely recorded in MBRN, or if not available by data on last menstrual period.

We did a separate evaluation on whether to include the children with congenital malformations in **Paper II** and **Paper III**. Registration of congenital malformations in MBRN constitute a

binary variable that include a variety of diagnoses, from genetic disorders that may significantly confound HI risk assessment to minor malformations and also conditions like patent ductus arteriosus (ICD-10 code Q25.0), which are unrelated to HI but common among preterm infants [253]. We therefore excluded children with congenital malformations in the term-born population in **Paper II**. However, we decided to include children with congenital malformations in **Paper III**, as excluding them would also exclude a large proportion of the most preterm infants with a patent ductus arteriosus. For both papers we included a reference population of term infants (GA ≥ 37 weeks). However, for **Paper II**, the reference population was further selected to include only non- admitted infants with Apgar 5-min scores 7-10.

3.3 Hearing assessments and outcomes

3.3.1 Paper I

Participants attended their study visit in the time period September 2017 and September 2018. Everyone underwent evaluation of middle ear status with otoscopy and tympanometry (Zodiac; Otometrics, Taastrup, Denmark), prior to pure tone audiometry. Tympanometry measures the pressure in the middle ear and the volume of the ear canal. By combining these two parameters it is possible to indirectly detect pathology in the tympanic membrane and middle ear, like fluid in the middle ear. The test is an important supplement to otoscopy for evaluating middle ear status. Tympanograms were classified as type A (normal), B (flat) and C (negative middle ear pressure).

In the gentamicin-exposed cohort, we collected urine samples for genetic analysis to identify carriers of the mitochondrial 1555A>G gene mutation. The Quick-DNA Urine Kit (Zymo Research, Irvine, CA) was used to extract DNA and the m.1555A>G mutation was analyed by using polymerase chain reaction amplification and melting curve analysis (LightCycler 480; Roche, Basel, Switzerland).

Pure tone audiometry thresholds were measured with the clinical audiometer Equinox 2.0, calibrated according to the specifications from the manufacturer, and with Equinox Suite 2.9.0 software (Interacoustics A/S, Middelfart, Denmark). Audiometry testing was performed by qualified audiology professionals with special attention to keep each child focused and avoid fatigue. The survey management software (Research Electronic Data Capture) was used to randomly decide if the left or right ear should be tested first. The conventional frequency range

(0.125–8 kHz) was tested first, using DD45 supra-aural earphones (RadioEar, Middelfart, Denmark) followed by testing in the EHF range (9–16 kHz) using HDA200 closed circumaural earphones (Sennheiser, Wedemark, Tyskland). Audiometry thresholds were acquired using a standard ascending technique and are expressed in dB HL.

The primary outcome for hearing was average thresholds in the conventional frequencies and the EHF-range. The pure tone average (PTA) was calculated for middle frequencies (0.5, 1, 2, and 4 kHz) using a standard method [254]. For the extended high-frequency (EHF) range, where no standard average like PTA exists, we averaged the six EHF frequencies (9, 10, 11.2, 12.5, 14, and 16 kHz), and termed it as the extended high-frequency average (EHFA). Since ototoxic effect usually affects both ears, we used PTA and EHFA from the better-hearing ear in the analysis. We defined a clinically significant HI as a PTA > 20 dB. The reported tympanogram results correspond to the better-hearing ear.

3.3.2 Paper II and III

The main outcome SNHI, was in both these papers defined by selected ICD-10 codes for HI registered in NPR or NIS. From NPR we included only diagnostic codes specific for sensorineural aetiology (H90.3-5), and to reduce potential false positive cases, a diagnosis of SNHI had to be recorded minimum twice in the NPR to be included as a study case. From NIS we also included the ICD-10 codes for conductive, mixed, and unspecified HI: The reason was that an explorative analysis showed that most HI cases in NIS were classified as "unspecific", supporting the assumption that diagnostic codes in NIS reflects the degree of disability, rather than diagnostic accuracy. The vast majority of HI-diagnoses in these two papers were from NPR, but we included also a few cases from NIS in order to optimise coverage. A Table listing all included diagnostic codes for HI is included supplementary files for **Paper II** and **Paper III**.

3.4 Predictors, confounders, mediators, and covariates

3.4.1 Paper I

The main predictor in this paper was gentamicin exposure in the neonatal period. This was assessed in two ways/by two different variables from medical files: the highest measured TPC of gentamicin (mg/L) and the cumulative gentamicin dose (mg/kg). Other recorded neonatal

variables included BW, GA, Apgar scores, neurologic abnormalities, mechanical ventilation, and any phototherapy for jaundice. Preterm infants have a higher risk of bilirubin-induced neurologic damage (BIND), experience harmful effects at lower levels of total serum bilirubin and receive more phototherapy compared to term infants [180, 255]. We therefore made an age-adjusted variable for bilirubin by using the peak total serum bilirubin level within the first two weeks of life and divided this value by GA in weeks. For the control group we recorded data on BW, admission to NICU for other reasons than infection, and any phototherapy for jaundice.

3.4.2 Paper II and III

All variables employed in these two papers were retrieved from MBRN, NPR or Statistics Norway and are displayed in **Table 3.**

Table 3. Neonatal and maternal variables included in the analyses (Paper II and III)

Medical Birth Registry of Norway *	**Norwegian Patient Registry ****	**Statistics Norway***
Neonatal • Infant sex • Birth weight • Birth length • Head circumference • Gestational age • SGA† • Apgar scores after 1, 5 and 10 minutes • Antibiotic therapy • Jaundice therapy • Non-invasive ventilation • Mechanical ventilation	**Neonatal** *Diagnostic (ICD-10) and procedural codes (NCMP)* • Neonatal sepsis (P 36) • Neonatal seizures (P90) • Intracranial haemorrhage (P52) • Therapeutic hypothermia (PXAB01)	
Maternal • Body mass index • Smoking in pregnancy • Parental consanguinity • Prolonged premature rupture of membranes • Mode of delivery	**Neonatal** *Diagnostic (ICD-10) and procedural codes (NCMP)* • Neonatal sepsis (P 36) • Neonatal seizures (P90) • Intracranial haemorrhage (P52) • Therapeutic hypothermia (PXAB01)	**Maternal** • Level of education • Immigrant status

* Data available for birth cohorts 1999-2014

** Data available for birth cohorts 2008-2014

† SGA; Being small for gestational age. Defined as birthweight < 10 percentile for gestational age

The main exposure in **Paper II** was perinatal asphyxia. Perinatal asphyxia was defined as having an Apgar 5-min score below 7 in combination with admission to NICU, this group was further subdivided into a moderate group with Apgar 5-min scores 4-6, and a severe group with scores between 0-3. Admission to NICU for term or near-term infants was interpreted as an indicator of neonatal compromise with symptoms that required monitoring and/or treatment. Infants with Apgar 5-min scores below 7, without admittance to the NICU, were considered to have experienced a "fast recovery" and were not categorized under perinatal asphyxia. NICU-admitted infants with Apgar 5-min scores ≥ 7 were classified in a separate exposure group termed “other neonatal morbidity”. For these four groups, data were available for all birth cohorts throughout the 16-year study period. The secondary exposure in **Paper II**, neonatal encephalopathy, was subdivided in two different groups: The first group, termed "neonatal encephalopathy with seizures," consisted of newborns who were admitted to the NICU with 5-min Apgar scores below 7 and diagnosed with neonatal seizures, but not treated with therapeutic hypothermia. The second group, termed "moderate-severe HIE," consisted of infants who underwent therapeutic hypothermia in line with the inclusion criteria from the original TOBY study protocol [166] and Norwegian guidelines [252].

The main exposure in **Paper III** was preterm birth and for this we defined three exposure groups based on the GA: i) moderate-late preterm (MLP) infants (GA 32-36 weeks), ii) very preterm (VP) infants (GA 28-31 weeks) and iii) extremely preterm (EP) infants (GA 22-27 weeks).

Other neonatal and maternal variables than those included in the definition of main exposures in **Paper II** and **Paper III**, were included in the models as confounders, mediators, and covariates (**Table 3**).

3.5 Statistical methods

3.5.1 Paper I

Sample Size and Power Calculation

Based on prior reports [256, 257] we estimated that we would find a mean EHFA threshold between ~5 to 10 dB in the healthy-control group. We expected to include 60-70% of the 357 invited gentamicin-exposed children in the final analysis. We considered a difference in EHFA thresholds of 10 dB or more, between groups to be clinically relevant. Including ~30 healthy controls and ~250 gentamicin-exposed children, would then give 80% power with a 2-sided 5% level of significance to detect a difference of 4-5 dB between the groups. From explorative analysis in the gentamicin-exposed group we knew that around half had a gentamicin TPC ≥1.0 mg/L, and the remaining a TPC< 1.0 mg/L. Thus 125 children in each group, would give 80% power with a 2-sided 5% level of significance to detect a difference of 3-4 dB between the groups.

Statistics

All clinical data were initially recorded into Research Electronic Data Capture (REDCap), a secure application developed to facilitate data collection for research studies (Vanderbilt University in Nashville, TN). Data analysis was done with IBM SPSS Statistics version 23 (IBM SPSS Statistics, IBM). Descriptive results are presented as medians and interquartile ranges (IQRs). To analye level of gentamicin exposure and other predictors that potentially could affect hearing thresholds [258] we used a univariable linear regression model. We included all predictors in a directed acyclic graph (DAG) and identified BW as a confounder in associations between all included predictors and hearing outcomes. We therefore adjusted each predictor separately for BW. Results from univariable and adjusted analyses are presented as regression coefficients with 95% confidence intervals (CIs).

3.5.2 Paper II and III

The SPSS software (28.0.1.0) was used for statistical analysis in both **Paper II** and **Paper III.** Results are presented as proportions, medians with interquartile range (IQR), or means with standard deviations (SD), as appropriate. To evaluate the association between SNHI and the exposure groups of interest we used logistic or binomial regression analysis with reference to the group of children defined as control group in each study.

In each paper we also analyzed the exposure of interest as a continuous variable; individual Apgar 5-min scores in **Paper II** and gestational weeks in **Paper III**.

We studied available literature on associations and pathophysiology between neonatal risk factors and SNHI [149, 170, 258], and drew DAGs to identify possible confounders, mediators, and other covariates in both study models.

Paper II

The DAG for **Paper II**, on asphyxia as predictor for SNHI, identified and defined intrauterine growth restriction and perinatal infection as potential confounders. We used the variable SGA to adjust for intrauterine growth restriction in the logistic regression analysis. For perinatal infection we considered that the available variables (systemic antibiotic therapy data from 1999-2014) and neonatal sepsis (data from 2008-2014), would overestimate the true prevalence of an infection, and potentially lead to overcorrection. We therefore restricted their use to the exploratory analysis. To investigate for possible differences between boys and girls we repeated the analysis with interaction term. Crude and adjusted odds ratios (ORs and aORs) are presented with 95% CIs.

Paper III

The DAG for **Paper III** (**Figure 7**), on preterm birth as predictor for SNHI, identified intrauterine growth restriction (represented by the variable SGA) as a possible confounder. We considered antibiotic therapy (associated with possible infection and/or ototoxicity), intracranial haemorrhage, jaundice therapy, non-invasive respiratory support, and mechanical ventilation as mediators.

To assess whether covariate effects depend upon level of prematurity, we conducted separate univariable binomial regression analyses for each strata of preterm infants: EP-infants, VP-infants, and MLP-infants. We also did an analysis with interaction terms for all mediators within each strata. In the main binomial regression analysis, we only adjusted for SGA. Comparisons of groups were performed with chi-square and non-parametric tests. Crude and adjusted risk ratios (RRs and aRRs) are presented with 95% CIs.

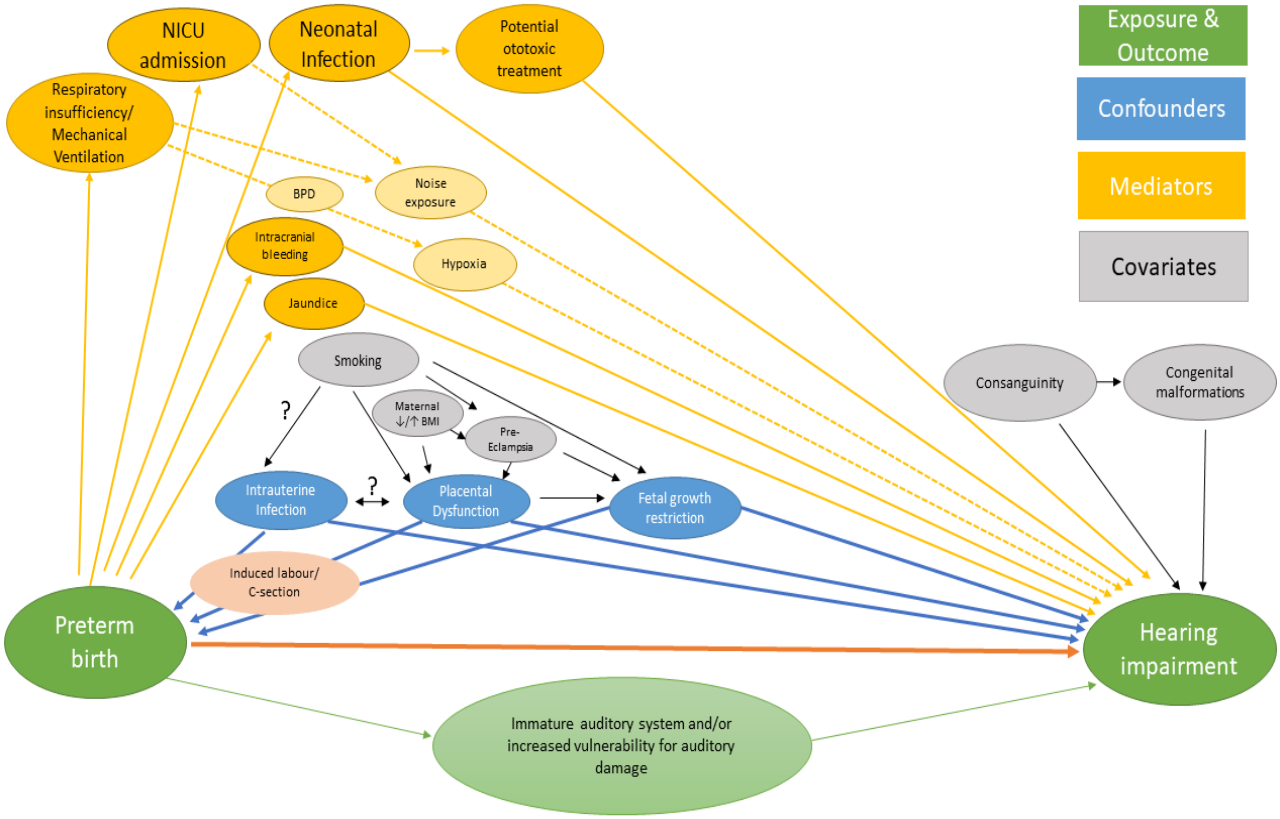


Figure 7. Directed acyclic graph (DAG) on associations between preterm birth and hearing impairment

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.

3.6 Approvals and study registration

3.6.1 Paper I

The study was approved by the Committee for Human Medical Research Ethics for Northern Norway (REK nr 2016/1786). A written informed consent form was signed by all parents, and age-appropriate written information about the study was provided to all participating children. The study was registered with www.clinicaltrials.gov (number NCT03253614) in August 2017.

3.6.2 Paper II and III

The studies and linkage between the five registries were approved by the Regional Ethical Committee for medical and health research ethics (REK nr. 2018/1789).

3.7 Funding

The funding for this project was provided by a scholarship from Northern Norway Regional Health Authority (grant number HN-1355-17). The clinical study in **Paper I** received a grant from Eckbo's legat for presentation of data. The projects in **Paper II** and **Paper III** received support from Gerda Meyer Nyquist Gulbrandson and Gerdt Meyer Nyquist's Fund, and the Norwegian SIDS and Stillbirth Society. The funders played no role in conducting the research, writing the papers or the thesis.

4 Summary of Main Results

4.1 Paper I

- A total of 226 (63%) of the 357 invited gentamicin-exposed children completed the study after parental consent.
- Eight children had relevant clinical HI. Those with known cause (3 with conductive- and 2 with genetic HI) were excluded. The remaining 3 cases were included in main analysis.
- High quality audiometry results were acquired for 219 children exposed to gentamicin as neonates and for 33 healthy non-exposed controls.
- The median (IQR) cumulative dose and TPC of gentamicin were 30 (24 to 42) mg/kg and 1.0 (0.7 to 1.2) mg/L, respectively.
- In the gentamicin exposed cohort: 75 (34%) were born preterm, 39 (17%) had a very low BW < 1500 g and 46 (20%) were treated with mechanical ventilation.
- The gene mutation, m.1555A>G was identified in one child (previously treated with gentamicin for 12 days) that had normal hearing (PTA 6 dB and EHFA 8 dB)
- The median (IQR) hearing thresholds in dB HL were within normal clinical range across all frequencies in both the gentamicin-exposed cohort; PTA 2.5 (0 to 6.25) and EHFA -1.7 (-5.0 to 5.0) and the control group; (PTA 2.5 (-0.6 to 3.8) and EHFA 4.2 (-5.9 to 0).
- Unadjusted statistical analysis showed a 2.5 dB absolute difference in median EHFA between groups, which was not statistically significant after adjustment for BW.
- Linear regression analysis, adjusted for BW, found that BW and tympanometry results were significant predictors for higher hearing thresholds in the conventional range and BW and prior treatment with tympanostomy tubes were significant predictors for higher hearing thresholds in the EHF range (**Table 4**).
- We found no significant association between the level of gentamicin exposure, neither the cumulative dose nor the TPCs, and hearing thresholds (**Table 4**).

Table 4. Regression analysis of gentamicin exposure and other predictors for hearing thresholds in the conventional mid-frequencies and extended high frequencies in the gentamicin-exposed cohort (n=219)

	Unadjusted		**Adjusted for birth weight**	
PTA threshold (best ear), dB HL	**Beta (95% CI)**	***P* value**	**Beta (9% CI)**	***P* value**
Gentamicin - cumulative dose	0.01 (-0.01 to 0.03)	0.35	-0.002 (-0.03 to 0.02)	0.83
Gentamicin - highest TPC	-0.17 (-1.4 to 1.1)	0.78	-0.03 (-1.2 to 1.1)	0.96
Birth weight - per 500 g	-0.4 (-0.7 to -0.1)	**0.004**		**< 0.02***
Mechanical ventilation	2.3 (0.7 to 3.9)	**0.004**	1.5 (-0.4 to 3.4)	0.13
Phototherapy	1.2 (-0.2 to 2.6)	0.10	0.02 (-1.6 to 1.7)	0.98
Peak bilirubin (n=161)	0.08 (-0.3 to 0.5)	0.68	-0.07 (-0.5 to 0.3)	0.72
Apgar 5 min < 6	0.7 (-1.1 to 2.5)	0.43	-1.1 (-2.9 to 0.7)	0.22
Small for gestational age	1.2 (-1.2 to 3.5)	0.33	0.4 (-2.0 to 2.7)	0.76
Age at study visit	-0.2 (-0.5 to 0.1)	0.17	-0.3 (-0.6 to 0.02)	0.07
Tympanostomy tubes	1.6 (-0.7 to 3.9)	0.18	1.4 (-0.9 to 3.7)	0.22
Tympanometry – best ear	-4.4 (-7.1 to -1.6)	**0.002**	-4.1 (-6.8 to -1.4)	**0.003**
EHFA threshold (best ear), dB HL	**Beta (CI)**	***P* value**	**Beta (CI)**	***P* value**
Gentamicin - cumulative dose	0.05 (0.01 to 0.08)	0.007	0.02 (-0.01 to 0.06)	0.21
Gentamicin - highest TPC	-0.6 (-2.5 to 1.3)	0.538	-0.29 (-2.2 to 1.6)	0.76
Birth weight - per 500 g	-0.9 (-1.3 to -0.5)	**<0.002**		**< 0.02***
Mechanical ventilation	4.6 (2.1 to 7.2)	**<0.001**	0.41 (- 0.6 to 5.5)	0.12
Phototherapy	3.6 (1.3 to 5.8)	**0.002**	1.5 (-1.2 to 4.1)	0.28
Peak bilirubin (n=161)	0.3 (-0.3 to 0.9)	0.38	-0.02 (-1.5 to 0.6)	0.96
Apgar 5 min < 6	1.7 (-1.2 to 4.6)	0.25	-2.5 (-5.4 to 0.3)	0.08
Small for gestational age	3.8 (0.01 to 7.5)	0.049	2.1 (-1.7 to 5.9)	0.28
Age at study visit	0.4 (-0.06 to 0.9)	0.08	0.3 (-0.2 to 0.8)	0.22
Tympanostomy tubes	9.1 (5.5 to 12.7)	**<0.001**	8.8 (5.3 to 12.2)	**< 0.001**
Tympanometry – best ear	-3.0 (-7.9 to 1.8)	0.22	-2.1 (-6.8 to 2.7)	0.39

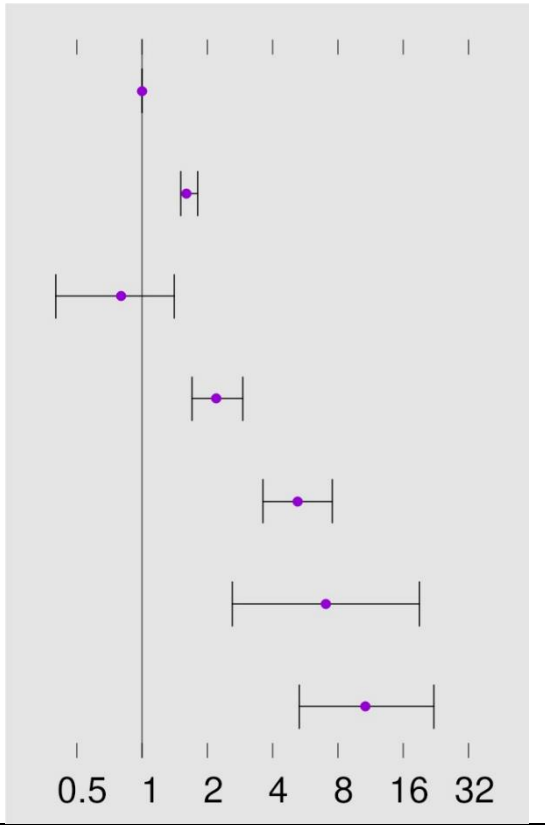
CI, confidence interval; EHFA, extended high frequency average; PTA, pure tone average; TPC, trough plasma concentration. * the *P* value for birth weight remained < 0.02 when adjusting for all predictors, except for a strong correlation between birth weight and mechanical ventilation, thus a P value of 0.12 and 0.13 for the PTA klland EHFA threshold respectively.

4.2 Paper II

- The study cohort constituted 866 232 children with GA ≥ 36 weeks; 7845 (0.9%) had Apgar 5-min score < 7, and among these 5563 (70.9%) were admitted to a NICU.
- The baseline prevalence of SNHI in the reference group was 0.6%.
- SNHI prevalence was increased in all admitted infants. There was an increasing prevalence along with increasing severity of asphyxia/encephalopathy, reaching 5.2% in infants with moderate-severe HIE (**Table 5**).
- Infants with severe asphyxia and encephalopathy were also most commonly treated with mechanical ventilation and antibiotics.
- The aOR for hearing impairment was for moderate asphyxia 2.2 (95% CI 1.7-2.9), severe asphyxia 5.2 (95% CI 3.6-7.5), neonatal encephalopathy with seizures 7.0 (95% CI 2.6-19.0), and moderate-severe HIE 10.7 (95% CI 5.3-22.0) (**Table 5**).
- Non-admitted infants with Apgar 5-min scores < 7 did not have increased OR of hearing impairment.
- In a separate analysis for confounders, covariates, and mediators the following remained associated with an increased aOR (95% CI) for SNHI: Mechanical ventilation 2.9 (1.4-5.9), being SGA 1.3 (1.2-1.4), neonatal jaundice therapy 1.2 (1.1-1.4), parental consanguinity 1.9 (1.5-2.3), daily smoking early in pregnancy 1.3 (1.2-1.5), and low maternal education 1.2 (1.2-1.3) (please see supplementary material **Paper 2**)
- The aOR for SNHI for individual Apgar 5-min scores in NICU infants increased with decreasing Apgar scores and reached 13.6 (95% CI 5.9-31.3) when the score was 0.

Table 4. Prevalence, crude, and adjusted odds ratio (OR) for sensorineural hearing impairment, in relation to perinatal asphyxia and neonatal morbidity, among 866 232 infants born ≥ 36 weeks gestation in Norway 1999-2014 and alive at two years of age.

Clinical description of exposure	Criteria	Hearing impairment N (%)	Crude OR (95 % CI)	Adjusted OR* (95 % CI)
Healthy reference group N=759 322	Apgar 5-min 7-10 No NICU admission	4 488 (0.6)	1.0 (reference)	1.0 (reference)
Neonatal illness - not asphyxia N=53 572	Apgar 5-min 7-10 NICU-admission	521 (1.0)	1.6 (1.5-1.8)	1.6 (1.5-1.8)
Low Apgar score, rapid recovery N=2 175	Apgar 5-min < 7 No NICU admission	10 (0.5)	0.8 (0.4-1.4)	0.8 (0.4-1.4)
Moderate asphyxia N=4 591	Apgar 5-min 4-6 NICU-admission	60 (1.3)	2.1 (1.2-2.7)	2.2 (1.7-2.9)
Severe asphyxia N=972	Apgar 5-min 0-3 NICU-admission	30 (3.1)	5.1 (3.5-7.3)	5.2 (3.6-7.5)
Neonatal encephalopathy with seizures† N=115	Apgar 5-min < 7 Neonatal seizures, no TH NICU-admission	4 (3.5)	7.2 (2.6-19.5)	7.0 (2.6-19.0)
Moderate-severe HIE † N=155	Received TH NICU-admission	8 (5.2)	10.9 (5.3-22.1)	10.7 (5.3-22.0)



†Data available only for birth cohorts 2008-2014 (N = 391 817)

* Adjusted for being small for gestational age

HIE; hypoxic-ischemic encephalopathy, min; minute, NICU; neonatal intensive care unit, TH; therapeutic hypothermia.

4.3 Paper III

- The study cohort consisted of 60 023 preterm infants: 2065 (3.4%) EP-infants, 6192 (10.3%) VP-infants and 51766 (86.2%) MLP-infants.
- The SNHI-prevalence was 0.7% in the term born reference group and 1.4% in the total preterm group. Within the preterm infant group, the SNHI-prevalence was markedly increased with lower GA, reaching 10% in infants born at GA 22-23 weeks.
- The SNHI-prevalence remained similar across all preterm infant groups comparing those born in the first (1999-2006) versus the second (2007-2014) 8-year time period.
- Rates of mechanical ventilation, antibiotic treatment and ICH were markedly higher with lower GA.
- In the univariable analysis, more variables were associated with increased risk for SNHI among MLP- and VP-infants than in EP-infants.
- The crude RR (95% CI) for SNHI increased from 1.7 (1.6-1.9) in MLP-infants, to 3.5 (3.0-4.1) in VP-infants and reached 7.9 (6.5-9.5) in EP-infants. Results remained similar after adjusting for SGA (**Table 6**).
- Analysis of smaller biweekly GA subgroups revealed a sharp rise in SNHI risk for the most immature groups, with aRRs of 11.8 (9.0-15.3) for infants born at 24-25 weeks GA and 14.8 (7.7-28.7) for those at 22-23 weeks GA (**Figure 8**).
- EP- and VP-infants received an SNHI diagnosis at significant earlier median age (around 1 year) than MLP-infants and term-born infants (around 4 years), $P < 0.002$.

Table 5. 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 w N=869 797	5 749 (0.7)	Reference	Reference
Moderate-late preterm infants, GA 32-36 w N=51 766	597 (1.2)	1.7 (1.6-1.9)	1.7 (1.5-1.8)
Very preterm infants, GA 28-31 w N=6 192	143 (2.3)	3.5 (3.0-4.1)	3.3 (2.8-3.9)
Extremely preterm infants, GA 22-27 w 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; w, weeks

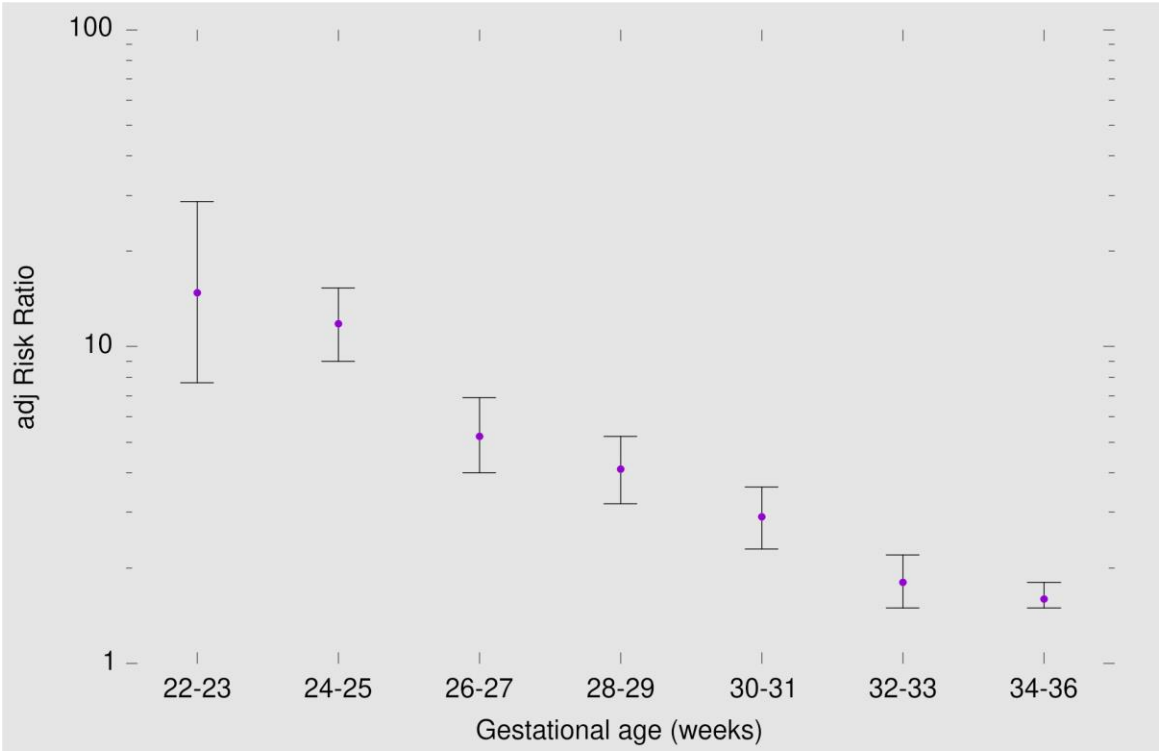


Figure 8. Adjusted* risk ratios (95% CI) for sensorineural hearing impairment according to weeks of gestation in preterm children born in Norway from 1999 through 2014, with reference to term-born infants.

*Adjusted for SGA

5 Discussion

The studies included in this thesis investigate three risk exposures in the neonatal period: gentamicin treatment (**Paper I),** asphyxia/neonatal encephalopathy (**Paper II**) and preterm birth (**Paper III**), and their subsequent risk for later childhood SNHI. Two different study designs were used. **Paper I** is a clinical follow-up study with detailed hearing evaluation among children recruited from a NICU cohort with retrospectively collected clinical and pharmacokinetic data on gentamicin use. **Paper II** and **Paper III** are population-based registry studies including all Norwegian births 1999-2014 with follow-up data on SNHI-diagnoses through 2019.

5.1 Sensorineural hearing impairment and risk factors

5.1.1 Prevalence of sensorineural hearing impairment

The total study population of **Paper II** and **Paper III**, representing all infants born 1999-2014 and alive at 2 years of age, had a baseline prevalence of SNHI at 0.7%. The control group in **Paper II** with exclusion of infants with congenital malformation and those admitted to NICU had a baseline SNHI- prevalence of 0.6%. Comparing these prevalence numbers with other population-based studies is challenging due to variations in subject age and definitions of HI. Recent studies with similar age ranges mainly report HI based on threshold levels or OAE results, without distinguishing between conductive HI and SNHI. This likely explains higher prevalence rates of 3-5% among nearly 7000 adolescents aged 12-16 years in the US National Health and Nutrition Examination Survey [259]. In contrast, a Canadian study that differentiated SNHI reported a prevalence in the age group 6-19 years of less than 2.2% [260].

Among all NICU admitted infants in **Paper II,** we found that a higher severity of asphyxia (by clinical defined categories) and by decreasing Apgar scores alone, were associated with a successive increase in SNHI-prevalence. Non-admitted infants with a 5-minute Apgar score below 7 did not have increased SNHI-prevalence. In our clinical categories of asphyxia, cooled babies with moderate-severe HIE had the highest SNHI-prevalence at 5.2%, which is in line with a reported pooled prevalence rate of 5 % in a recent systematic review assessing risk of HI after TH [174].

In **Paper III**, we found an SNHI-prevalence of 1.4% among preterm infants, which was double that of the term reference group. The prevalence rates increased by lower GA and was 5.2% among EP-infants, but more than 10% among the most immature babies born before 25 weeks gestation. Our findings align with two recent large studies from Poland and The Netherlands, which reported HI rates ranging from 1-2% in preterm infants with GA 31-32 weeks, increasing to 7-11% in those with GA 24-25 weeks [146, 147].

In **Paper I**, among the gentamicin-exposed cohort of 219 children, we found 3 (1.4%) children with clinically relevant SNHI. This cohort may be also considered a quite typical NICU cohort, in which many infants receive antibiotics.

5.1.2 Aminoglycosides and gentamicin therapy

In **Paper I** we performed a detailed audiological analysis, assessing hearing thresholds in both the conventional and the extended high frequencies. After adjustment for other potential neonatal risk factors for SNHI we did not find any association between the level of gentamicin exposure and hearing thresholds in school-age (median follow up was 9 years).

Previous studies also report a low risk of ototoxic induced HI after gentamicin treatment in the newborn period, regardless of dosing regimen [261–263]. This is supported by a large American multicenter cohort study involving 84,808 infants, which showed no association between gentamicin treatment and hearing screening failures at discharge [126]. However, most results come from observational and retrospective studies with a paucity of detailed hearing evaluation and very few studies present long-term data on hearing outcomes. Fuchs presented 5-year follow up data on hearing (including diagnostic ABR and VRA or play audiometry), in a small case-control study and found no significant difference in gentamicin exposure in 25 VLBW infants with SNHI and their normal hearing controls [264]. An older study from the 1970s reported four-year hearing outcomes after newborn aminoglycoside therapy, assessed using play audiometry (0.5-4 kHz). Only 25% of the original cohort was evaluated at four years, but they found no significant aminoglycoside-related HI [265].

In **Paper II** and **Paper III,** we had data on whether neonatal antibiotic therapy was administered, but without specification on the type of antibiotic and duration. However, in Norway, the majority of antibiotic prescriptions to neonates admitted to a NICU include gentamicin [266, 267]. We therefore consider that the dichotomous variable “antibiotic use” is

associated with gentamicin exposure yes/no. In **Paper II** antibiotic therapy was markedly more common in admitted infants with Apgar 5-min score 0–3 and infants with neonatal encephalopathy, both severe clinical conditions often treated empirically with antibiotics. We found that antibiotic therapy doubled risk for SNHI in the *total* study population, but significance was lost when the analysis was adjusted for severe perinatal asphyxia. In **Paper III**, the percentage of preterm infants treated with antibiotics increased progressively with decreasing gestational age (across the categories from MLP-, to VP-, and then to EP-infants). Antibiotic therapy was only identified as a predictor of SNHI in infants born after 28 weeks gestation, and the associated risk was stronger with higher GA. Antibiotic treatment without confirmed infection is reported to be more common among the most preterm infants [268]. The observed pattern of associations in **Paper III** may therefore reflect the severity of underlying conditions rather than antibiotics themselves.

Sepsis, a primary indication for gentamicin treatment, involves a complex host response to infection that can damage multiple organs. Experimental models have shown that systemic inflammation can increase ototoxicity both due to an enhanced cochlear absorption of gentamicin but also that sepsis alone without additional ototoxic influence can cause SNHI [269, 270]. An association between sepsis and risk for subsequent HI is also reported in the adult population [271, 272]. Cross found a higher rate of hearing screen failures in gentamicin-exposed neonates diagnosed with sepsis or severe inflammation, although this could also be attributed to treatment for a longer time [273].

Infections are also suggested to affect outcomes in infants with neonatal encephalopathy and moderate-severe HIE, which may be relevant to the risk associations explored in **Paper II**. However, a recent systematic review found no conclusive evidence whether perinatal infection may affect neurological outcome following newborn encephalopathy or not but noted the low quality of existing studies and the need for further research [274]. This illustrates the potential complex interplay between infections and established risk factors for SNHI.

Considering that sepsis may independently increase risk for SNHI, studies on aminoglycoside ototoxic effects should preferably account for culture-proven infections. Puia- Dumitrescu's large study on neonatal gentamicin treatment demonstrated an association between culture-proven infections and failed hearing screenings, but not between gentamicin use and hearing outcomes [126].

The mechanisms behind gentamicin-induced ototoxicity in neonates and children are incompletely understood [129]. Evidence of aminoglycoside ototoxicity is more established in older children than in neonates [275]. This could be because older children, such as those with cystic fibrosis or cancer, over time can receive larger cumulative doses than neonates [107, 109, 276]. Alternatively, the neonatal inner ear might be less susceptible to ototoxic damage, or the ototoxic effects of gentamicin in neonates might be partially reversible. Regenerative capacity of hair cells after ototoxic damage, including from aminoglycosides, has been demonstrated in the neonatal mammalian cochlea [277–279]. This observed capability of hair cell regeneration is attributed to fetal properties that are only present early in the neonatal period.

Genetic predisposition for aminoglycoside-induced hearing impairment

Recently a rapid point-of-care genotyping test for the m.1555A>G variant was introduced [280]. The test can detect the presence of this variant in neonates before aminoglycosides are prescribed, but there is still insufficient evidence to conclude if such testing is clinical and cost efficient [281]. A UK study found that the test did not delay the onset of antibiotic treatment [280] but these results, obtained from two large NICUs, may not be generalizable to smaller NICUs or other settings. The key uncertainty is the actual risk and severity of aminoglycoside-induced HI in neonates with the m.1555A>G variant. Notably, the majority (70-80%) of neonates with this mutation pass initial hearing screenings and subsequent tests after aminoglycoside treatment [135, 282, 283]. Although this does not eliminate the possibility of later-onset HI, case reports, from our **Paper I** and others, show individuals with the m.1555A>G variant maintaining normal hearing despite significant exposure to aminoglycosides. In **Paper I** one patient with m.1555A>G variant had normal hearing in school age after receiving a cumulative gentamicin dose of 72 mg/kg in the newborn period. Al-Malky similarly reported normal hearing in an eleven-year-old child with the same mutation after repeated aminoglycoside treatments [284]. In contrast, a Finnish study reported that 10 of 19 children with the m.1555A>G genetic variant, and normal hearing at birth, developed SNHI during childhood without exposure for aminoglycosides [285]. These findings indicate a complex interplay between genetic predisposition and environmental factors in determining auditory outcomes and illustrates the need for further research to fully assess the value of rapid genotyping in preventing aminoglycoside-induced HI in neonates.

5.1.3 Low Apgar scores, asphyxia and encephalopathy

In **Paper II** we found that among neonates admitted to a NICU, lower 5-min Apgar scores and more severe neonatal encephalopathy, were associated with a progressively higher risk of SNHI. The inverse relation between the Apgar 5-minute scores and later risk of SNHI is also reported in an older Norwegian birth cohort, though this study lacked clinical data for assessment of neonatal encephalopathy [169].

The highest risk for SNHI in **Paper II** was found in cooled infants with moderate-severe HIE, consistent with many other studies reporting a markedly higher prevalence in this group [173, 174]. Given the widely used diagnostic criteria for moderate-severe HIE requiring hypothermic treatment [166], these infants constitute a relatively well-defined subgroup allowing for more direct comparisons with other studies.

Studies assessing the risk of SNHI after perinatal asphyxia, using other exposure variables than HIE report more conflicting results [170, 258, 287]. A Dutch multicenter study of 11,000 NICU infants found that Apgar 5-min scores < 7 did not predict failed hearing screenings at discharge, but in this study data on neonatal encephalopathy were lacking [286]. In contrast a smaller French study reported that an Apgar 5-min score predicted a failed hearing screen but did not adjust for preterm birth or other risk factors [287]. Inconsistent results are likely due to variations in terms and definitions of perinatal asphyxia across papers and can also reflect variations in study populations: When Apgar scores are used in populations with preterm infants or those with congenital malformations [170, 287] the predictive value is shown to be lower [288].

In **Paper I** we also assessed Apgar scores but found no association between 5-min scores less than 6 and hearing thresholds. This is likely because infants with moderate and severe HIE, and presumably the lowest Apgar scores, were rarely included in this study cohort. The reason for this is that local guidelines recommend other antibiotics than gentamicin to infants with severe asphyxia and those with HIE who receive TH, due to risk for impaired renal function and possible increased risk for gentamicin-ototoxicity in infants with moderate-severe HIE [173].

5.1.4 Prematurity and low birth weight

In **Paper III** we found an inverse association between GA and RRs for SNHI, and a markedly increase in risk in the most immature EP-infants born before 26 weeks gestation, with RRs of passing 15 in those born 22-23 weeks. These risk trends align with many large studies that report a steep rise in neurodevelopmental impairment rates, including HI, as gestational age decreases in the most immature infants [289]. High rates of HI in the preterm population are reported in many studies. Two previous register-based Norwegian studies also demonstrated an inverse relationship between both BW and GA, and later risk for SNHI [290, 291]. However, the effect of GA was lost in analyses adjusted for both predictors. Since gestational age and birth weight are often strongly correlated, adjusting for birth weight might obscure the true effect of gestational age on HI [292]. This adjustment could also suggest that growth retardation independently affects the risk for SNHI, a finding also observed in our preterm cohort. In contrast, the UK Millennium Cohort Study reported no association between GA or BW and later risk for HI, linking the risk solely to neonatal illness [293]. Reason for this discrepancy may be that the study used parent-reported data for both HI and neonatal illness, whereas our study used more detailed, physician-reported data for these variables.

In the gentamicin exposed study cohort in **Paper I,** 34% were born preterm. Among the three detected cases of SNHI that were included in the analysis, two of the cases were born preterm and before 28 weeks gestation. This equals a SNHI-prevalence of 2.7% in the preterm AURORA-study cohort. The vast majority of the preterm children had normal clinical hearing, but a key finding from **Paper I** was that low BW was associated with poorer hearing thresholds in both the conventional and EHF range. This can indicate that preterm children may have a subclinical affection of hearing, that might make them more vulnerable to HI later in life.

Adults born preterm have increased risks for many chronic disorders, affecting overall health outcomes from childhood into adulthood [294]. Several studies have shown an association between low BW and HI in adulthood [13], though it's unclear if this represents HI with onset in childhood. Additionally, a recent study has demonstrated that low BW predicts an increased risk for HI with adult onset [295]. This suggests that individuals born prematurely may have an increased vulnerability for developing HI later in life, in addition to the higher prevalence of HI observed in childhood.

5.1.5 Other risk factors; interactions and synergies

A central question in all three papers is to what extent co-morbidity related to our primary exposures affected the overall risk for SNHI: A number of conditions and therapies associated with neonatal intensive care are identified as risk factors for HI including being born SGA, ICH, hyperbilirubinemia, infections, respiratory diseases, mechanical ventilation and noise exposure. Many studies also indicate that synergistic effects of several harmful exposures are more important than single risk factors [112, 170, 287, 296].

Respiratory disease and complications necessitating mechanical ventilation are common in neonatal intensive care and associated with increased risks of neurodevelopmental impairments. Respiratory insufficiency is also frequently reported to predict risk for HI in [170, 189, 190, 297, 298]. However, it remains uncertain if respiratory insufficiency is an independent risk factor for SNHI. In **Paper I** mechanical ventilation was associated with higher hearing thresholds in the unadjusted analysis, but not after adjustment for BW. In **Paper II** mechanical ventilation remained a significant risk factor for SNHI in the total study population after adjustment for severe perinatal asphyxia, and in **Paper III** it significantly increased the risk for SNHI among preterm infants except those born before 28 weeks.

Hyperbilirubinemia is recognized for its ototoxic potential, particularly in preterm infants [178, 180]. While extreme hyperbilirubinemia, reaching transfusion thresholds, is well established as a risk factor for SNHI, the risks associated with lower levels remain less defined [299]. We assessed hyperbilirubinemia in all three papers and found that it overall had a low association with risk for SNHI. In **Paper I** we found no association between (age adjusted) serum bilirubin levels and SNHI. In **Paper II** infants who had received phototherapy remained with a slightly increased risk (OR 1.2) for SNHI in the total study population after adjustment for severe perinatal asphyxia. Among preterm infants in **Paper III,** only MLP-infants who had received phototherapy had increased risk (RR 1.4) for SNHI.

In **Paper III**, many of the assessed risk factors (antibiotic therapy, mechanical ventilation, hyperbilirubinemia and SGA), did not increase risk for SNHI in EP-infants. In this group, ICH was the only independent risk factor for SNHI, an association also reported by others [300]. A possible explanation is that the risk linked to prematurity itself has a relatively higher contribution among the most immature infants and thus obscuring the effect from co-morbidities and invasive therapies. However, it could also be due to the very high prevalence of most of these comorbidities and therapies, resulting in insufficient statistical power to detect

existing associations. SGA, however, has due to its definition an equal prevalence in all subgroups, and was also not identified as an independent risk factor in EP-infants, in contrast to in VP- and MLP-infants. The causes of SGA are diverse, and varying underlying etiologies may explain the differences in risk for neurodevelopmental outcomes among SGA infants [301, 302]. For example, cCMV can affect fetal growth and is associated with SGA and is also strongly linked to SNHI [303]. Although we lacked data on cCMV infection, this example underscores how understanding the specific causes of SGA can facilitate more accurate analysis and interpretation of its risk associations.

Noise exposure is a well-documented and common cause of SNHI [304]. Research has shown that noise levels in many NICUs often exceed the recommended 45 dB limit set by the American Academy of Pediatrics [305, 306]. Some evidence suggests that noise could also exacerbate the ototoxic effects of aminoglycoside antibiotics used in NICUs and potentially act synergistically with other neonatal risk factors for SNHI like hypoxia and hyperbilirubinemia [104, 305, 307]. We did not have data on noise exposure for any of the papers. However, a paper on respiratory support in preterm infants from the NICU in Tromsø showed that both nasal high flow therapy and continuous positive airway pressure, both widely used therapies in preterm infants, led to ambient noise levels at 70-74 dB [308].

In summary the contribution of the different risk factors differed in our three papers, and in the different subpopulations of sick neonates. The relationships and underlying mechanisms connecting various morbidities and treatments in neonates are highly complex and largely unknown. It is therefore plausible that associations are likely to vary among/ across different neonatal populations. For instance, the indication for mechanical ventilation in a term infant (such as asphyxia or malformation) will differ from the indication in a preterm infant (such as RDS).

5.2 Defining hearing outcomes in research

Research on neonatal risk factors for SNHI shows significant variation in diagnostic methods and definitions of HI. Many studies use the results of UNHS as an indicator of, or to define, HI [126, 309, 310]. However, a positive screening result is not diagnostic for HI, nor does it indicate severity or differentiate between conductive and SNHI. Newborn hearing screening tests also tend to have lower specificity in high-risk infant populations and a higher rate of false positives in preterm infants compared to term infants [311, 312]. Other studies use auditory brainstem response results to define HI [190, 258], but these can also include false positives

due to conductive HI, which is more common in NICU populations, or cases that improve or resolve as preterm infants mature [313]. The fitting or use of a hearing aid as measure of HI, is a commonly used to define HI in large neurodevelopmental follow-up studies of preterm infants and in randomized trials of TH [314–317]. While fitting of a hearing aid is a concise definition of HI with high correlation to functional loss, it can exclude HI cases that commonly is not treated with hearing aids, such as mild HI, unilateral HI and possibly also cases with severe HI in children with multiple disabilities, where comorbidities may complicate or contraindicate the use of hearing aids. This is likely the reason why the Swedish Express study, which use hearing aid fitting to define HI, reports a much lower prevalence of HI at 2.2% in EP-infants compared to the prevalence of 5.2% as observed in our **Paper III**.

Parent-reported outcomes to assess hearing is also used to define HI, e.g. in the UK Millennium Cohort Study [293]. While this may be effective for confirmed cases, the method may fail to detect undiagnosed HI as research shows that parents frequently overlook or underestimate their children's HI [318], and potentially result in an underreported overall risk.

For **Paper II** and **Paper III,** we used diagnostic codes retrieved from the NPR and NIS. A main limitation with using ICD-10 coded for hearing impairment is that they do not include well defined diagnostic criteria, as hearing levels in dB or affected frequency range, and has not been validated against audiometry results. From NPR we only included cases registered two times (twice), to assure a more certain diagnosis of permanent SNHI. Still the lack of well-defined diagnostic criteria increases the risk for individual variations in the diagnostic assessment and accuracy among physicians. This may explain why we found a higher overall prevalence of SNHI in our study population than reported from other Scandinavian studies [45, 47]. However, a possible overestimation should still not affect the calculated ORs or RRs for the different risk groups in **Paper II** and **Paper III**.

Even though pure tone audiometry constitutes the gold standard for hearing assessment, it is rarely used in studies assessing neonatal risk factors for HI. This probably reflect young age of children in the study population, but also that pure tone audiometry thresholds are more resource-intensive to both measure and collect. Pure tone thresholds are available in some regional health registries and are used to report prevalence [45]. The recently established Norwegian registry for hearing in children aims to systematically collect data on pure tone thresholds [319]. For detecting ototoxicity, EHF audiometry (**Paper I**), is the most sensitive subjective testing method, with potential to also detect subclinical hearing damage before it

becomes evident in the conventional hearing range [106, 320]. It has also been used in other studies on ototoxicity in children [107, 109].

When assessing childhood HI in research, sufficient follow-up time is important in order to detect progressive [46] and/or late-onset HI, reported in 13-33% of children with HI [229, 321]. Sufficient follow-up duration is especially important in studies on high-risk infants, constituting the target population in this thesis. In preterm children it is known that the auditory function can be unstable, and both improve and deteriorate over time [193], illustrating the need for a long-term follow-up in this population in order to achieve optimal estimates for both prevalence and severity of SNHI. In **Paper II** and **Paper III,** we recorded SNHI-diagnosis during minimum five years observation period after birth. In **Paper III** we also assessed the median age of diagnosis between different preterm groups and the control group. In contrast to previous reports [192, 193] we found no indication for increased risk for late-onset SNHI in our preterm cohort. On the contrary, the EP- and VP-infants had an established SNHI-diagnosis at a younger age than more mature infants.

Sufficient follow-up duration for reliable risk estimates is also important when assessing ototoxicity. For childhood ototoxic HI a delay between exposure and SNHI is well known after treatment with platinum chemotherapy [322, 323]. Delayed onset SNHI has also been suggested in sporadic cases after neonatal treatment with gentamicin [324, 325]. In **Paper I** we had a median follow time of 9 years, and this is to our knowledge the first long-term follow-up study performing high quality pure tone audiometry and EHF audiometry to assess ototoxicity after neonatal exposures.

5.3 Increased surveillance of high-risk groups

The JCHI guidelines from 2019 recommend increased audiologic surveillance for subgroups of infants with known neonatal risk factors for HI [113]. This includes NICU-admission for more than 5 days, aminoglycoside treatment for more than 5 days and a diagnosis of asphyxia/HIE, particularly if receiving TH. A recent systematic review investigated neonatal risk factors in relation to late-onset and progressive SNHI [114] and concluded that NICU admissions for more than 5 days and specific risk factors like mechanical ventilation, preterm birth (< 34 weeks) increased risk for late-onset SNHI. [114]. The authors therefore suggest audiological follow up in these groups, but without referring to documentation for yield of such surveillance.

Based on our findings in **Paper I**, adding to previous research reporting low risk for ototoxic damage after neonatal gentamicin treatment, targeted surveillance after this treatment is, in our opinion, not indicated. In **Paper II** and **Paper III,** we had data on NICU admission but could not investigate correlations between SNHI and length of NICU stays as this information was not available.

The majority of children with late onset SNHI do not have any known risk factors [326–328] and the best strategy to detect late-onset SNHI is an ongoing debate. Many researchers argue that there is both limited and conflicting evidence for risk factor-based surveillance programs in childhood [326, 329, 330]. A recent study reported that targeted screening in children based on speech and language delays and parental or professional concern, detected more late-onset cases than neonatal risk factors [326]. This could suggest that focusing on these indicators of HI, within existing broader developmental surveillance programs for high-risk infants, might be more effective than targeted audiological surveillance based solely on specific risk factors. This is also supported by our findings in **Paper III** where the EP-infants in Norway, that are included in a general developmental follow-up program for preterm children [331], received their SNHI diagnosis at a significant earlier median age than more mature infants with SNHI.

5.4 Methodological considerations

5.4.1 Internal validity

Internal validity refers to how well a study accurately identifies the true relationship between variables without influence from methodological errors [332]. To achieve high internal validity, central sources for systematic error as selection bias, information bias and confounding must be reduced.

5.4.1.1 Selection bias

Selection bias refers to the type of error that can occur when the participants included a study are not representative of the target population [333]. Selection bias can be caused by the method used to include or invite participants, but also because prerequisites and motivation to participate can vary among individuals.

For the clinical study in **Paper I**, the target population was a previous studied clinical cohort of 440 infants treated with gentamicin as neonates. We invited 357 patients of these to participate in our study by letter. Among these, 226 responded with consent and completed the study, constituting a total response rate of 63% which is considered acceptable and thus increases the likelihood that the sample is representative of the population [334, 335]. We excluded 83 children from the original cohort from invitation due to death, severe medical condition making participation difficult or new address outside catchment area. Because of higher rate of severe perinatal morbidity in this uninvited group, we questioned whether these children differed in their neonatal characteristics and thus our exposure variables of interest: To assess the representativeness of the follow-up cohort, we compared data from the original population-based study cohort, which included all gentamicin-exposed neonates over an 8-year period (n=440), with the follow-up cohort (n=226). There were no significant differences between the two cohorts in terms of BW, proportion of VLBW infants, cumulative gentamicin doses, highest median TPCs, or the proportion of children with gentamicin TPCs exceeding 2.0 mg/L.

Norway has several national compulsory health registries with high coverage [336]. Observational data from these registries, can be linked and enables research across entire birth cohorts over longer time periods. This was the method for **Paper II** and **Paper III.** The mandatory registration of all births in the MBRN and the comprehensive coverage of key exposure variables such as GA, BW and Apgar scores help ensure that selection bias is low in **Paper II** and **Paper III**. After linking the data, selecting the final study cohorts and defining the control groups introduces a new risk for selection bias. For example, by including only infants alive at 2 years of age to ensure adequate follow-up, we potentially exclude the infants with most severe perinatal morbidity, who biologically might be at a higher risk for HI. However, from a clinical perspective, conditions resulting in death do not influence long-term outcomes, as the opportunity for long-term outcomes no longer exists.

For **Paper III** we also excluded children with birth weight Z- scores outside 3 SD, which could impose a risk for excluding some infants with severe growth restriction. To assess this, we did exploratory analysis which showed that the majority (80 %) of children excluded due to these Z-score criteria had Z scores > 3 SD. Thus, we believe that most of these children were misclassified due to either incorrect BW or GA and excluding them actually decreased the risk for bias. This also illustrates the importance of exploratory analysis when handling data and making choices for the selection of the final study population and variables.

5.4.1.2 Information bias

Information bias is a systematic error caused by inaccurate measurement or classification of exposure, covariate, or outcome variables in a study [332].

Paper I was a retrospective cohort study where exposure variables were collected from medical records. Even though this process involves some risk for information bias, we believe that the risk is low due to a relatively small cohort and well-defined, and quantitative variables. The audiological outcome variables in **Paper I** were measured and collected according to a well-defined study protocol, as previously described, and should represent minimal risk for information bias.

All maternity and neonatal health care in Norway is public, with well-established clinical routines for measurement and registration of the baseline variables (GA, BW and Apgar scores) in MBRN that constituted the exposure variables of **Paper III** and **Paper III**.

Potential ototoxic exposure was assessed in all papers. We had access to detailed data regarding gentamicin dosing and therapeutic drug monitoring in **Paper I.** In **Paper II** and **Paper III,** we assessed the dichotomous MBRN-variable "neonatal antibiotic use", with no details on type of antibiotic, length of treatment or serum concentrations.

Some of the variables from MBRN, such as smoking habits before and during pregnancy and maternal BMI, pose a higher risk for information bias. The high number of missing data for these variables suggests that it may have been challenging to record them in routine care, and that they may have been omitted or forgotten during the clinical consultation. Additionally, variables like smoking habits are susceptible to recall bias, as pregnant women, aware of the risks to the baby, may be influenced by feelings of guilt or shame, which could skew their responses. However, for **Paper II** and **Paper III**, the most central risk associated with BMI and smoking would be growth retardation and placental insufficiency, that we also were able to assess by other variables like e.g. SGA.

5.4.1.3 Confounding

Confounding refers to when a third factor influences both the exposure and the outcome of a study, potentially distorting the observed association. For a factor to be a confounder, it must be associated with both the exposure and the outcome, and not be an intermediary variable in the causal pathway between exposure and outcome. To reduce confounding, the variable

identified as confounder should be adjusted for. The causal pathways between the neonatal exposure variables studied in this thesis are potentially complex as previously discussed. To identify possible confounders, we drew DAGs for all three papers and adjusted for these in the main analysis. Still, residual confounding must be accounted for in all three papers.

5.4.2 External validity

External validity, also known as generalizability, is the extent to which the findings and conclusions from a study population can be applied to the general population outside the studied cohort. In **Paper I**, the clinical study cohort was drawn from a NICU servicing/treating all infants born with a GA < 32 weeks and all newborns in need for intensive care like mechanical ventilation, in the two northernmost counties in Norway (Troms and Finnmark). This cohort is likely representative of the Norwegian newborn population requiring neonatal intensive care. However, factors such as comorbidities, other ototoxic medications, and varying levels of noise, which can influence the ototoxic effects of gentamicin, can differ across neonatal care practices internationally and by region. Additionally, the prevalence of neonatal morbidities like asphyxia may also vary between high-, middle- and low-income countries. Given these variations and the small size of our study cohort, further long-term follow-up studies using EHF audiometry in diverse NICU settings are important to verify the consistency of our results. To our knowledge, **Paper I** is the first study to perform long-term audiological follow-up with EHF audiometry after neonatal gentamicin treatment, also underscoring the need for replication in other NICU populations to confirm the findings.

The study cohorts for **Paper II** and **Paper III** consisted of national birth cohorts, making results representative of the entire Norwegian infant population. However, when the study period spans many years, changes in clinical practice and survival rates can affect results. To address this in **Paper III**, we compared the rates of SNHI in preterm infants born in the first and last 8-year epochs of the study cohort. The findings revealed similar rates, concomitant with stable survival rates for EP-infants in Norway during the same period, as reported by Stensvold et al. [337]. Some associations are more generalizable, like the association between neonatal disease (biological exposure) and HI (disease outcome). Other outcomes like age of first diagnosis, depending on the national healthcare system and practices, resulting in lower generalizability of these findings. As previously discussed, prevalence rates based on diagnostic codes, which reflect national clinical practices, may not be generalizable outside Norway. However, the ratios between risk groups should remain unaffected.

6 Ethical considerations

All studies included in this thesis are considered well within ethical standards, and all were approved by a regional ethical committee.

The study in **Paper I** involved clinical visits for participating children and their guardians, this included various tests, but none were invasive or uncomfortable procedures. We supplied the information for guardians with age-appropriate written information for all children, and all study consultations were conducted by experienced clinical staff. Eight children were found to have a clinical HI and five of these had known aetiology. All these were provided with individualized clinical follow-up as appropriate. One child was identified with the m.1555A>G genetic variant and was referred to genetic counselling.

Paper II and **Paper III** were based on anonymized observational data without any contact with study subjects. However, to ensure adequate data protection all data were handled in research servers with secured access.

7 Conclusions and future perspectives

Preterm birth and perinatal asphyxia/neonatal encephalopathy were in **Paper II** and **Paper III** identified as independent risk factors for SNHI, and the risk was inversely correlated with increasing clinical severity of these two central neonatal morbidities. For both preterm birth and perinatal asphyxia, the SNHI- prevalence similarly reached 5% in the groups with highest clinical severity (EP-infants and cooled infants with moderate-severe HIE, respectively). Invasive therapies and comorbidities increased the risk for HI among both infants with asphyxia and those born preterm, but predominantly in infants born after 28 weeks. Low BW was also associated with poorer hearing thresholds in school age in **Paper I**, in line with the finding of preterm birth as an independent risk factor for SNHI in **Paper III**. Gentamicin is widely used both in preterm and term infants with suspected or confirmed infections. In **Paper I,** hearing outcomes in school age of children exposed to gentamicin in the neonatal period were assessed by EHF audiometry, a sensitive method for detecting ototoxicity. We found no association between gentamicin therapy and clinical or subclinical SNHI in school age.

The potential, but low risk of aminoglycoside-induced ototoxicity must be evaluated alongside the adverse effects of broad-spectrum antibiotics in neonates with increased antibiotic resistance development [338]. Further research into otoprotective drugs to prevent potential aminoglycoside-induced ototoxicity [129] and drug formulations with lower toxicity [131] could therefore be important strategies for further reducing the use of broad-spectrum antibiotics like 3rd generation cephalosporins and carbapenems. The results of **Paper I** indicates a low risk of gentamicin-induced ototoxicity in neonates, but more studies are needed to confirm these results and to clarify how genetic predisposition, noise and other comorbidities and treatments may affect the risk for ototoxicity.

Damage to hearing early in life is of particular concern, as childhood HI can impact language and overall development. More studies on peri- and neonatal risk factors, with the combination of high-quality and long-term follow-up data on hearing outcomes, is needed. This can be facilitated through greater interdisciplinary collaboration between pediatric and audiological professional communities. Access to high quality hearing data can be more easily enabled through dedicated health registries, such as the recently founded Norwegian national register for all children with HI, established in 2022 [319] and the Norwegian neonatal network register, which provides more extensive and accurate data on neonatal illness and treatment than MBRN. Combining data from specialized registries like these can enable studies of high quality. General awareness and understanding of the impact of HI in high-risk groups, such as survivors of asphyxia and preterm birth, are also important from both a clinical and scientific perspective. This can be achieved by increased clinical attention to HI in high-risk children, and by including hearing outcomes more comprehensively in clinical studies on neurodevelopmental outcomes after neonatal insults.

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Paper I

Hemmingsen, D., Mikalsen, C., Hansen, A.R., Fjalstad, J.W., Stenklev, N.C. & Klingenberg, C. (2020).

Hearing in Schoolchildren After Neonatal Exposure to a High-Dose Gentamicin Regimen.

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Hearing in Schoolchildren After Neonatal Exposure to a High-Dose Gentamicin Regimen

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abstract

OBJECTIVE: To assess the association between gentamicin exposure in the neonatal period and hearing in school age.

METHODS: This study included children exposed to a high-dose (6 mg/kg) gentamicin regimen as neonates (2004–2012), invited for follow-up at school age, and a healthy age-matched control group. We assessed hearing with pure tone audiometry including the extended high-frequency (EHF) range. Outcomes were average hearing thresholds in the midfrequencies (0.5–4 kHz) and the EHFs (9–16 kHz). The measures of gentamicin exposure were cumulative dose and highest trough plasma concentration. We used linear regression models to assess the impact of gentamicin exposure, and other peri- and postnatal morbidities, on hearing thresholds.

RESULTS: A total of 219 gentamicin-exposed and 33 healthy-control children were included in the audiological analysis. In the gentamicin cohort, 39 (17%) had a birth weight <1500 g. Median cumulative doses and trough plasma concentrations were 30 (interquartile range 24–42) mg/kg and 1.0 (interquartile range 0.7–1.2) mg/L, respectively. Median hearing thresholds for the midfrequencies and the EHFs were 2.5 (0 to 6.3) dB hearing level and −1.7 (−5.0 to 5.0) dB hearing level, both of which were within the normal range. In an adjusted analysis, increasing hearing thresholds were associated with lower birth weight and postnatal middle-ear disease but not level of gentamicin exposure. After adjusting for birth weight, there was no difference in hearing threshold between the gentamicin-exposed cohort and healthy controls.

CONCLUSIONS: Exposure to a high-dose gentamicin regimen in the neonatal period was not associated with an increase in hearing thresholds in schoolchildren being able to complete audiometry.

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The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation, to any qualified researcher.

Dr Hemmingsen conceptualized and designed the study, conducted the initial analysis, wrote the first draft of the manuscript, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis; Ms Mikalsen collected data and reviewed and revised the manuscript; Mr Hansen collected data, conducted the initial analysis, and reviewed and revised the manuscript; Dr Fjalstad reviewed all gentamicin data, established the cohort from the neonatal period, contributed to statistical analyses, and revised the manuscript; Dr Stenklev provided substantial contribution to the study design and interpretation of the data and reviewed and revised the manuscript; (Continued)

WHAT'S KNOWN ON THIS SUBJECT: Evidence for ototoxic hearing loss after gentamicin exposure is mainly from studies in adults and older children. Neonatal studies report low rates of ototoxicity but have commonly used only moderately sensitive hearing tests.

WHAT THIS STUDY ADDS: We performed pure tone audiometry, including the extended high-frequency range, in 219 schoolchildren (median age 9 years) exposed to a high-dose gentamicin regimen in the neonatal period. We found no association between exposure to gentamicin and hearing levels.

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Gentamicin is widely used for the treatment of neonatal sepsis.[1,2] Extended-interval dosing regimens are currently recommended.[3] To ensure effective therapy, it is necessary to attain a high circulating dose, and some experts suggest that each dose should be as high as 7.5 mg/kg because of the large distribution volume in neonates.[4] There is still uncertainty about the optimal dosing regimen and safety, in particular regarding potential ototoxicity.

Ototoxic hearing loss typically first affects the high frequencies (>8 kHz), may then progress to involve lower frequencies, and is usually bilateral and irreversible.[5,6] Neonates admitted to NICUs have up to a 10-fold increase in prevalence of hearing loss.[7,8] Prolonged gentamicin treatment and high trough plasma concentrations (TPCs) have been suggested to increase the risk of ototoxicity.[3,9,10] Prematurity and low birth weight, severe perinatal morbidities, other ototoxic drugs, and environmental noise are also risk factors for hearing loss.[8,11–13] These factors will often coexist with gentamicin treatment, making it difficult to delineate which risk factor is of greatest clinical importance.

Current evidence indicates a low risk of hearing loss after gentamicin treatment in neonates.[5,14,15] However, data are limited by several factors. The objective testing methods used in newborn hearing screening (otoacoustic emissions or automated brainstem audiometry) evaluate hearing at frequencies between 2 and 6 kHz and do not detect mild hearing loss or early signs of ototoxicity. Moreover, most studies have evaluated hearing shortly after exposure to gentamicin and could not identify late-onset or progressive hearing loss.

Pure tone audiometry in the extended high-frequency (EHF) range is the most sensitive subjective testing method to detect ototoxic hearing loss even before it becomes evident in the conventional hearing range.[16,17] For this method, children must be able to cooperate.[18,19] In this study, we performed a hearing assessment of schoolchildren exposed to a high-dose gentamicin regimen in the neonatal period to assess long-term safety.

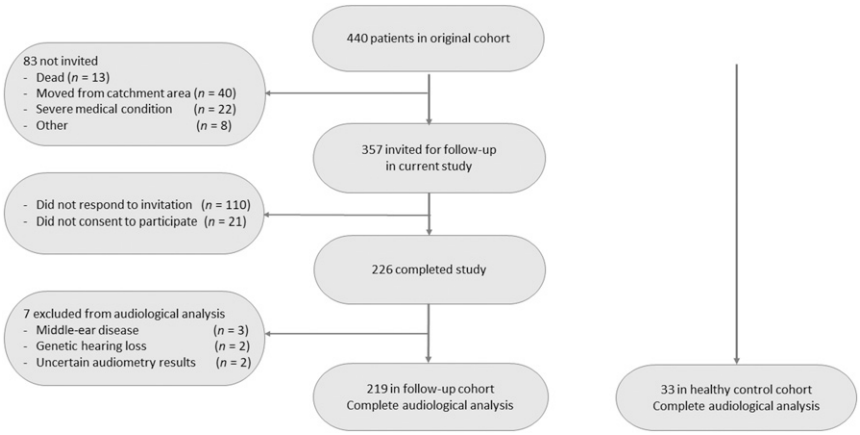

FIGURE 1
Participant flow diagram. The final study populations, from the original cohort through exclusions, are displayed.

METHODS

Setting, Study Design, and Participants

Children included in this study had been admitted to the NICU at the University Hospital of North Norway and received gentamicin therapy between 2004 and 2012. This NICU is the only unit offering care for infants born before 32 weeks' gestation and all other newborn infants (≥32 weeks' gestation) in need of mechanical ventilation or intensive care in the 2 northern-most counties in Norway. We previously validated our extended-interval, high-dose (6 mg/kg) gentamicin dosing regimen in 440 neonates who were exposed to at least 3 doses of gentamicin between 2004 and 2012.[20] The vast majority of TPCs (94%) were within the normal range, there was a low rate of prescription error, and we found no evidence of early-onset ototoxicity using a transient evoked otoacoustic emissions screening test before hospital discharge.[20]

For the current study (Fig 1), 357 children from the original cohort were invited for a detailed hearing assessment at age 6 to 14 years. We also, from public primary schools, recruited a control group of 33 healthy children with no history of previous use of aminoglycosides and no previous hearing problems or tympanostomy tubes. Parents of all children filled out a questionnaire including any history of middle-ear infections, treatment with tympanostomy tubes, or use of intravenous antibiotics after the neonatal period.

Neonatal Characteristics

For the gentamicin-exposed cohort, we collected data on birth weight, gestational age (GA), Apgar scores, neurologic abnormalities, mechanical ventilation, and any phototherapy for jaundice. Preterm neonates are more susceptible to bilirubin-induced neurologic damage, suffer adverse effects at lower total serum bilirubin (TSB) levels, and receive more phototherapy than term infants.[21,22] We recorded the peak TSB level within the first 2 weeks of life and divided this value by GA in weeks, creating an age-adjusted variable of possible bilirubin toxicity instead of

using crude peak TSB levels. To assess level of gentamicin exposure during hospitalization, we recorded 2 variables: the highest measured gentamicin TPC (mg/L) and the cumulative gentamicin dose (mg/kg). For the healthy-control group, we collected data on birth weight, admission to a NICU for reasons other than infection, and any phototherapy for jaundice.

Baseline Investigations

Participants attended 1 study visit between September 2017 and September 2018. We did otoscopy and tympanometry at 226 Hz (Zodiac; Otometrics, Taastrup, Denmark) before pure tone audiometry. Tympanogram results were classified as type A (normal), B (flat), and C (negative pressure). We collected a urine sample for analysis of the mitochondrial 1555A>G gene mutation in all gentamicin-exposed children. DNA was extracted by using the Quick-DNA Urine Kit (Zymo Research, Irvine, CA). The m.1555A>G gene mutation was analyzed by using polymerase chain reaction amplification and melting curve analysis (LightCycler 480; Roche, Basel, Switzerland).

Audiometric Data Acquisition

Pure tone audiometry thresholds were measured with the Equinox 2.0 clinical audiometer by using Equinox Suite 2.9.0 software (Interacoustics A/S, Middelfart, Denmark). The audiometer was calibrated according to the manufacturer's specifications and in accordance with International Organization for Standardization references.[23,24] We used the DD45 supra-aural earphones (RadioEar, Middelfart, Denmark) for the conventional frequencies (0.125–8 kHz) and Sennheiser HDA200 closed circumaural earphones (Sennheiser, Wedemark, Germany) for the EHFs (9–16 kHz). Testing was done first in the conventional frequency range before the EHF range. We used the ascending method to acquire thresholds.[25] Special care was taken for each child to avoid fatigue and loss of concentration. The first ear tested (left or right) was randomly assigned by the survey management software (Research Electronic Data Capture). Audiometry testing was done by a trained audiologist or an audiology-trained ear-nose-throat physician. The hearing thresholds are expressed as dB hearing levels (HLs).

Audiological Outcomes

The main audiological outcomes were average hearing thresholds in the conventional frequencies and the EHF range. We calculated the established pure tone average (PTA), representing the mean of the conventional midfrequencies (0.5, 1, 2, and 4 kHz), according to an established reference method.[26] There is no established equivalent to PTA in the EHF range. We chose to use the average of all 6 EHFs (9, 10, 11.2, 12.5, 14, and 16 kHz), hereafter termed the extended high-frequency average (EHFA). Middle-ear problems can be unilateral, but ototoxic hearing losses are most often bilateral. Thus, we used the PTA and EHFA for the best ear in the final analysis. A relevant clinical hearing loss was defined as PTA and/or EHFA threshold >20 dB in the best ear. We report tympanogram results corresponding to the best-ear result.

Ethics and Trial Registration

The study was approved by the Committee for Human Medical Research Ethics for Northern Norway. All parents signed a written informed consent form, and all participating children received age-appropriate written information about the study. The study was registered with www.clinicaltrials.gov (number NCT03253614) in August 2017.

Sample Size and Power Calculation

On the basis of previous studies,[27,28] we estimated that the mean EHFA threshold would be ~5 to 10 dB in the healthy-control group. We realistically hoped to include 60% to 70% of the 357 invited gentamicin-exposed children. We considered that a 10 dB difference in the EHFA hearing threshold would represent a clinically relevant difference between healthy controls and the gentamicin-exposed group. By including ~30 healthy controls and ~250 gentamicin-exposed children, we would have 80% power with a 2-sided 5% level of significance to detect a difference of 4 to 5 dB between the groups. Moreover, within the group of gentamicin-exposed children, we knew that approximately half of them had a gentamicin TPC ≥1.0 mg/L, and the rest had a TPC <1.0 mg/L. With 125 children in each group, we would have 80% power with a 2-sided 5% level of significance to detect a difference of 3 to 4 dB between the groups.

Data Analysis and Statistics

All clinical data were first entered into Research Electronic Data Capture, a secure, Web-based software platform designed to support data capture for research studies (Vanderbilt University, Nashville, TN). Clinical and audiometry data were analyzed by using IBM SPSS Statistics version 23 (IBM SPSS Statistics, IBM Corporation). Descriptive results are expressed as medians and interquartile ranges (IQRs). We used a univariable linear regression model to analyze level of gentamicin exposure and other predictors that may affect hearing thresholds.[29] We then plotted all predictors in a directed acyclic graph, and on the basis of clinical and biological knowledge, we identified birth weight as the central confounder of both the outcome and other predictor variables. Finally, we adjusted each predictor separately for birth weight. Results from univariable and adjusted analyses are presented as regression coefficients with 95% confidence

TABLE 1 Children With Hearing Loss, Defined as PTA Threshold >20 dB HL (n = 3) and/or EHFA Threshold >20 dB HL (n = 5)

Age, y	PTA (Best Ear), dB HL	EHFA (Best Ear), dB HL	Clinical Characteristics	Gentamicin TPC, mg/L	Gentamicin Cumulative Dose, mg/kg	Included Main Audiological Analysis
12	14	22	GA 41 wk; middle-ear effusion	3.5	66	No
14	14	38	GA 32 wk; middle-ear effusion	1.2	30	No
7	21	NA	GA 39 wk; middle-ear effusion	1.8	24	No
9	18	41	Twin, GA 28 wk; mild psychomotor delay of unknown cause; genetic hearing loss diagnosed at school age	0.3	72	No
9	58	55	Twin, GA 28 wk; mild psychomotor delay of unknown cause; genetic hearing loss diagnosed at school age	0.3	54	No
12	46	49	Twin, GA 24 wk; long respiratory support; hearing loss diagnosed at age 8 y	0.6	72	Yes
9	6	28	GA 26 wk; normal middle ear; no mechanical ventilation	0.7	108	Yes
6	15	21	GA 41 wk; admitted to NICU for observation, no perinatal complications; normal middle ear but previous tympanostomy tubes	0.9	18	Yes

NA, not available.

intervals (CIs). We defined P <.05 as significant.

RESULTS

After parental consent, 226 of 357 (63%) gentamicin-exposed children were included. Eight children had relevant hearing loss (Table 1). Five of these had known etiology (3 with ongoing middle-ear disease and 2 with developmental delay and genetic hearing loss) and were therefore not included in the main audiological analysis. The 3 remaining children had hearing loss of uncertain etiology and were included in the main audiological analysis. Two more children were excluded from the main audiological analysis because of obvious lack of concentration during testing with uncertain validity of audiometry results.

High-quality audiometry results were obtained for 219 children exposed to gentamicin in the neonatal period and for 33 healthy controls (Table 2). In the gentamicin cohort, 39 (17%) had very low birth weight (VLBW) (<1500 g birth weight), and 46 (20%) had been treated with mechanical ventilation. One child was diagnosed with a m.1555A>G gene mutation. This child had culture-confirmed group B streptococcal early-onset sepsis and received gentamicin for 12 days but had normal audiometry results (best-ear thresholds: PTA 6 dB and EHFA 8 dB). Three term children who underwent therapeutic hypothermia because of severe perinatal asphyxia also received gentamicin; all 3 later had normal psychomotor development and no hearing loss.

TABLE 2 Background Characteristics, Gentamicin Exposure Data, and Audiometry Results

Variables and Results	Gentamicin Cohort (n = 219)	Control Cohort (n = 33)
Age, y, at study visit, median (IQR)	9 (7–11)	10 (9–12)
Female sex, n (%)	84 (38.4)	17 (51.5)
Birth wt, g, median (IQR)	3360 (2154–3896)	3500 (3239–3816)
<1500, n (%)	39 (17.8)	
1500–2499, n (%)	25 (11.4)	
≥2500, n (%)	155 (70.8)	
GA, wk, median (IQR)	39 (33–41)	No information
≤31, n (%)	47 (21.5)	
32–36, n (%)	28 (12.8)	
≥37, n (%)	144 (65.8)	
Small for GA, <10th centile, n (%)	19 (8.7)	0 (0%)
Mechanical ventilation, n (%)	46 (21)	0 (0%)
Apgar score 5 min, median (IQR)	9 (7–10)	No information
Phototherapy, n (%)	71 (32.4)	3 (10)
Neurologic abnormalities as neonates, n (%)	13 (5.9)	0 (0%)
Intracranial hemorrhage	8 (3.7)	
Cystic periventricular leukomalacia	3 (1.4)	
Meningitis	3 (1.4)	
Gentamicin TPC, mg/L, median (IQR)	1.0 (0.7–1.2)	NR
TPC <1 mg/L, n (%)	128 (58.4)	
TPC ≥1 mg/L, n (%)	91 (41.6)	
Gentamicin cumulative dose, mg/kg, median (IQR)	30 (24–42)	NR
≤30 mg/kg (3–5 doses), n (%)	111 (50.7)	
≥36 mg/kg (6 doses or more), n (%)	108 (49.3)	
m.1555 G>A mutation, n (%)	1 (0.5)	Not tested
Tympanostomy tubes, any, n (%)	19 (8.7)	0 (0%)
PTA threshold (best ear), dB HL,[a]* median (IQR)	2.5 (0–6.25)	2.5 (−0.6 to 3.8)
EHFA threshold (best ear), dB HL,[b]** median (IQR)	−1.7 (−5.0 to 5.0)	−4.2 (−5.9 to 0)

NR, not relevant.

[a] P = .33 (adjusted analysis for birth weight; gentamicin-exposed cohort versus healthy-control cohort).

[b] P = .10 (adjusted analysis for birth weight; gentamicin-exposed cohort versus healthy-control cohort).

* P = .10 (unadjusted analysis; gentamicin-exposed cohort versus healthy-control cohort).

** P < .02 (unadjusted analysis; gentamicin-exposed cohort versus healthy-control cohort).

Overall, the gentamicin-exposed cohort and the control group had normal hearing thresholds for the whole frequency range (Table 2, Fig 2). Unadjusted statistical analysis showed a 2.5 dB absolute difference in median EHF hearing thresholds between the gentamicin-exposed children and healthy controls, which is not of clinical significance. After adjusting for birth weight, the statistical difference was lost (Table 2). No International Organization for Standardization references exist for the EHF range in children. We compared our results with data from the hitherto largest published reference study, which included 90 healthy children and adolescents aged 5 to 19 years.[30] EHF hearing thresholds between groups from the current study and the reference study were comparable (Fig 2).

Tables 3 and 4 display the linear regression analysis of predictors for hearing thresholds in the conventional midfrequencies and EHFs. In the conventional midfrequencies, we found that birth weight, mechanical ventilation, and tympanometry results were all significant predictors in the unadjusted analysis. After adjusting each predictor for birth weight, only birth weight and tympanometry result remained significant predictors. In the EHFs, we found that cumulative gentamicin dose, birth weight, phototherapy, being small for GA, mechanical ventilation, and tympanostomy tubes were significant predictors in the unadjusted analysis. After adjusting each predictor for birth weight, only birth weight and tympanostomy tubes remained significant predictors.

TABLE 3 Regression Analysis of Gentamicin Exposure and Other Predictors for Hearing Thresholds in the Conventional Midfrequencies in the Gentamicin-Exposed Cohort (n = 219)

PTA Threshold (Best Ear), dB HL	Univariable		Adjusted for Birth Wt	
	β (95% CI)	*P*	β (95% CI)	*P*
Gentamicin, cumulative dose	.01 (−0.01 to 0.03)	.35	−.002 (−0.03 to 0.02)	.83
Gentamicin, highest TPC	−.17 (−1.4 to 1.1)	.78	−.03 (−1.2 to 1.1)	.96
Birth wt per 500 g	−.4 (−0.7 to −0.1)	.004	—	<.02[a]
Mechanical ventilation	2.3 (0.7 to 3.9)	.004	1.5 (−0.4 to 3.4)	.13
Phototherapy	1.2 (−0.2 to 2.6)	.10	.02 (−1.6 to 1.7)	.98
Peak bilirubin (n = 161)[b]	.08 (−0.3 to 0.5)	.68	−.07 (−0.5 to 0.3)	.72
Apgar 5 min <6	.7 (−1.1 to 2.5)	.43	−1.1 (−2.9 to 0.7)	.22
Small for GA	1.2 (−1.2 to 3.5)	.33	.4 (−2.0 to 2.7)	.76
Age at study visit	−.2 (−0.5 to 0.1)	.17	−.3 (−0.6 to 0.02)	.07
Tympanostomy tubes	1.6 (−0.7 to 3.9)	.18	1.4 (−0.9 to 3.7)	.22
Tympanometry, best ear	−4.4 (−7.1 to −1.6)	.002	−4.1 (−6.8 to −1.4)	.003

—, not applicable.

[a] The *P* value for birth weight remained <.02 when adjusting for all predictors except for a strong correlation between birth weight and mechanical ventilation; thus, *P* = .13 for this adjusted analysis.

[b] Peak bilirubin adjusted for gestational age.

We compared data from the population-based original study cohort, including all gentamicin-exposed neonates during the 8-year study period (n = 440), with data from the follow-up cohort (n = 226) to assess the representativeness of the follow-up cohort. There were no differences in birth weight, the

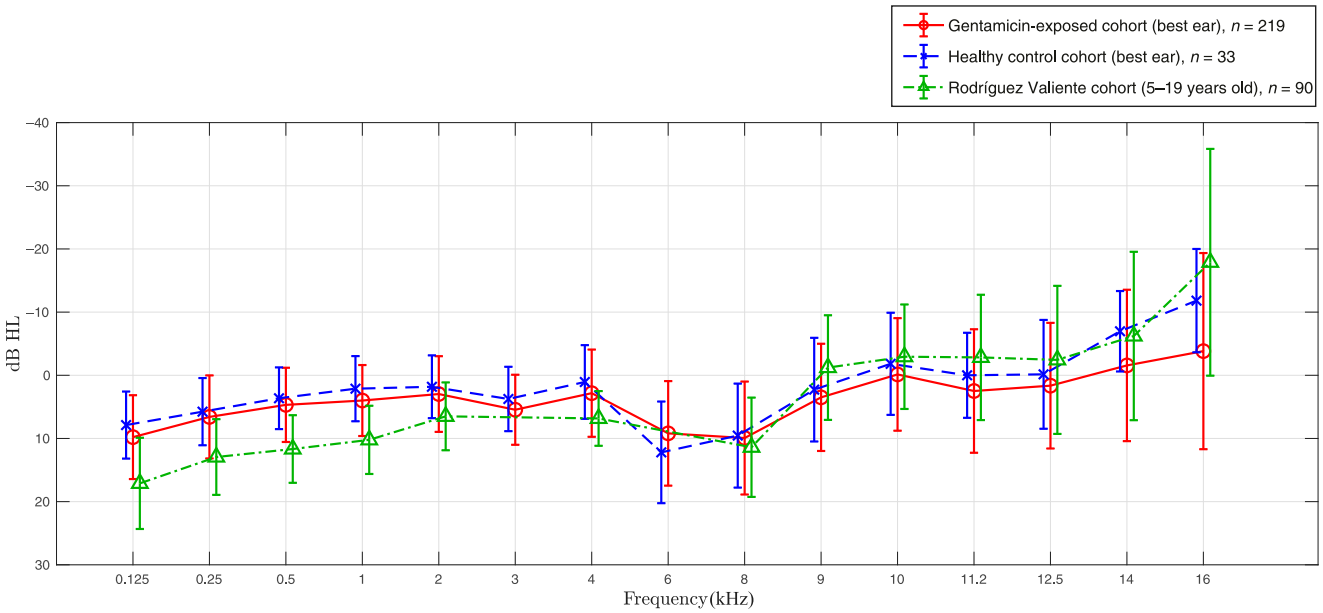

FIGURE 2
Hearing thresholds in dB HL (mean and SD) in the conventional and EHF range in the gentamicin-exposed cohort, healthy controls, and a reference population.[30]

TABLE 4 Regression Analysis of Gentamicin Exposure and Other Predictors for Hearing Thresholds in the EHFs in the Gentamicin-Exposed Cohort (n = 219)

EHFA Threshold (Best Ear), dB HL	Univariable		Adjusted for Birth Wt	
	β (95% CI)	*P*	β (95% CI)	*P*
Gentamicin, cumulative dose	.05 (0.01 to 0.08)	.007	.02 (−0.01 to 0.06)	.21
Gentamicin, highest TPC	−.6 (−2.5 to 1.3)	.54	−.29 (−2.2 to 1.6)	.76
Birth wt per 500 g	−.9 (−1.3 to −0.5)	<.001	—	<.02[a]
Mechanical ventilation	4.6 (2.1 to 7.2)	<.001	.41 (−0.6 to 5.5)	.12
Phototherapy	3.6 (1.3 to 5.8)	.002	1.5 (−1.2 to 4.1)	.28
Peak bilirubin (n = 161)[b]	.3 (−0.3 to 0.9)	.38	−.02 (−1.5 to 0.6)	.96
Apgar 5 min <6	1.7 (−1.2 to 4.6)	.25	−2.5 (−5.4 to 0.3)	.08
Small for GA	3.8 (0.01 to 7.5)	.049	2.1 (−1.7 to 5.9)	.28
Age at study visit	.4 (−0.06 to 0.9)	.08	.3 (−0.2 to 0.8)	.22
Tympanostomy tubes	9.1 (5.5 to 12.7)	<.001	8.8 (5.3 to 12.2)	<.001
Tympanometry, best ear	−3.0 (−7.9 to 1.8)	.22	−2.1 (−6.8 to 2.7)	.39

—, not applicable.

[a] The *P* value for birth weight remained <.02 when adjusting for all predictors except for a strong correlation between birth weight and mechanical ventilation; thus, *P* = .12 for this adjusted analysis.

[b] Peak bilirubin adjusted for gestational age.

proportion of VLBW infants, cumulative gentamicin doses, the highest median gentamicin TPCs, and the proportion of children with gentamicin TPC >2.0 mg/L between the 2 cohorts (Supplemental Table 5).

DISCUSSION

Our main objective in this study was to perform a detailed hearing assessment of schoolchildren exposed to a high-dose gentamicin regimen in the neonatal period to assess potential clinical or subclinical signs of ototoxic hearing loss as markers of long-term harm or safety. We tested hearing in both the conventional frequencies and the EHFs, adjusted findings for other potential peri- and postnatal risk factors for hearing loss, and compared audiological data with those of a healthy-control cohort. We found no association between level of gentamicin exposure in the neonatal period and hearing thresholds after 9 years median follow-up time.

Previous studies and reviews indicate a low risk of gentamicin-induced ototoxicity in the newborn period regardless of dosing regimen. However, there is a paucity of long-term, detailed follow-up studies. One recent case-control study compared level of gentamicin exposure in 25 VLBW infants who presented with hearing loss during the first 5 years of life and a matched control group without hearing loss and found no differences in gentamicin exposure between groups.[31] One study from the 1970s reported 4-year follow-up hearing results after newborn aminoglycoside therapy using play audiometry (0.5–4 kHz). Only 25% of their original cohort were assessed at 4 years, but the authors did not identify any substantial aminoglycoside-attributable hearing loss.[32] Our study is the first long-term follow-up study performing high-quality pure tone audiometry, including the EHFs, of children exposed to gentamicin in the newborn period. A delay between exposure and hearing loss is well known from platinum-induced hearing loss in children.[33,34] This has also been suggested in sporadic cases after neonatal treatment with gentamicin.[35,36] We found no indication of late-onset gentamicin-induced ototoxicity in our study.

The mechanisms behind gentamicin-induced ototoxicity are not fully understood.[37] Currently, there is stronger evidence for aminoglycoside ototoxicity in older children than in neonates.[6,18,19] A possible explanation is that older children (eg, with cystic fibrosis or cancer) receive larger cumulative doses than those commonly administered in neonates.[6,18,19] Alternatively, the newborn inner ear is less vulnerable to ototoxicity or gentamicin-induced ototoxicity, so these effects may be partly reversible. Indeed, reversible ototoxic effects from aminoglycosides have been demonstrated in animal models.[38] Moreover, transient hearing loss in neonates is reported and could be explained by a transient cochlear dysfunction due to inflammation[39] or a delayed maturation of the auditory system.[40] However, in our study cohort, there were no signs of ototoxicity either at NICU discharge or at follow-up in children exposed to gentamicin.

Hearing loss in infants admitted to NICUs has a prevalence of ∼2% to 4% compared with 0.1% to 0.3% in the general newborn population.[7,29,41,42] Low GA, VLBW, mechanical ventilation, perinatal infections, hyperbilirubinemia, and severe asphyxia are all identified as risk factors for hearing loss.[8,11,13] In line with other studies, we found a strong association between decreasing birth weight and increasing hearing thresholds.[14] Some authors argue that low birth weight itself does not cause hearing loss[43] but is rather associated with other perinatal factors that more directly affect hearing. We evaluated other possible predictors for hearing, such as Apgar scores, hyperbilirubinemia and/or phototherapy, and mechanical ventilation, but none of these were associated with increasing hearing thresholds after adjusting for birth weight.

The m.1555A>G mutation is associated with hearing loss, in particular after exposure to aminoglycoside antibiotics.[44] In our cohort, only 1 patient (0.44%) had this mitochondrial mutation, and this patient had normal hearing despite a cumulative gentamicin dose of 72 mg/kg. In another cohort of infants treated with gentamicin, 4 of 436 (0.9%) had a mitochondrial

12sRNA mutation, but only 1 showed evidence of possible hearing loss.[45] Some authors suggest testing for mitochondrial mutations before neonatal aminoglycoside treatment.[46] A clinical study is planning to assess rapid pharmacogenetic testing of the m.1555A>G mutation to avoid aminoglycoside therapy in at-risk neonates.[47] However, given the low and variable prevalence of this mutation in different ethnic populations combined with a variable penetrance, this approach may not be justified or cost-effective in all settings.[44,48,49]

Middle-ear disease in childhood may cause mechanical hearing loss because of permanent inflammatory damage and/or sensorineural hearing loss secondary to toxic effects on the inner ear.[50,51] Isolated sensorineural hearing loss in the EHFs after otitis media is also reported in children.[52] We found a significant association between previous tympanostomy tubes, which is a marker for more severe middle-ear disease, and EHF hearing thresholds. We also found increased hearing thresholds in the conventional midfrequencies in children with negative middle-ear pressure. The latter may reflect a subtle mechanical hearing loss caused by ongoing middle-ear pathology.

The strength of our study is the unique long-term audiological data that are sensitive enough to detect subtle and subclinical hearing loss. We also present data on different levels of gentamicin exposure, with cumulative dose being the most important proxy for exposure, but found only a weak correlation between cumulative dose and EHF-thresholds, which was not significant after adjusting for birth weight (Table 3, Supplemental Fig 3). It is a paradox that most neonatal gentamicin dosing regimens recommend lower gentamicin doses (4–5 mg/kg) than those of older children (7 mg/kg) despite a proportionally higher distribution volume in neonates.[4] Since 2004, we have used a dosing regimen with a fixed gentamicin dose (6 mg/kg) for all neonates and a variable dosing interval (24–48 h) depending on GA and postnatal age.[20] This dosing regimen has a low risk of prescription errors.[20] Our study also has limitations. Children from the original cohort with the most severe comorbidities were not included in our follow-up because of clinical conditions that made them unable to complete audiometric testing. Some of these children may have hearing problems in addition to other disabilities. However, we are only aware of 1 child from the original cohort, who was diagnosed with a congenital cytomegalovirus infection, who has a cochlea implant. Since 2009, our unit has avoided routine use of gentamicin in children with severe asphyxia who undergo therapeutic hypothermia. Therefore, only 3 children with this condition were included in the follow-up cohort, all 3 of whom had normal hearing. There are conflicting results on a possible association between gentamicin exposure and hearing loss in children with severe perinatal asphyxia who have undergone therapeutic hypothermia.[53,54] Only 10% of the children in our study received >10 doses (>60 mg/kg) of gentamicin, and we cannot exclude that long courses of gentamicin have a greater ototoxic potential, also in the neonatal period. Finally, a response rate of 63% adds potential selection bias. Still, the gentamicin exposure data and the proportion of VLBW infants were similar in the original and follow-up cohorts.

CONCLUSIONS

In schoolchildren with no severe disabilities and who were therefore able to complete a detailed hearing assessment, we found no association between neonatal exposure to a high-dose, extended-interval gentamicin regimen and increased risk of hearing loss in the conventional midfrequencies and EHFs. Increasing hearing thresholds were associated with lower birth weight and middle-ear disease in childhood, but the vast majority of children had normal hearing. Potential damage to hearing early in life is of great concern because childhood hearing loss, and prelingual hearing loss in particular, may affect both language and general development.[55] It is therefore important to provide high-quality, long-term follow-up data on hearing after gentamicin exposure in neonates because this drug is widely used in neonates, and safety is therefore paramount.

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ABBREVIATIONS

CI: confidence interval
EHF: extended high frequency
EHFA: extended high-frequency average
GA: gestational age
HL: hearing level
IQR: interquartile range
PTA: pure tone average
TPC: trough plasma concentration
TSB: total serum bilirubin
VLBW: very low birth weight

Dr Klingenberg conceptualized and designed the study, coordinated and supervised data collection, directed all phases of the study, revised the final manuscript, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered at www.clinicaltrials.gov (identifier NCT03253614).

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Hearing in Schoolchildren After Neonatal Exposure to a High-Dose Gentamicin Regimen

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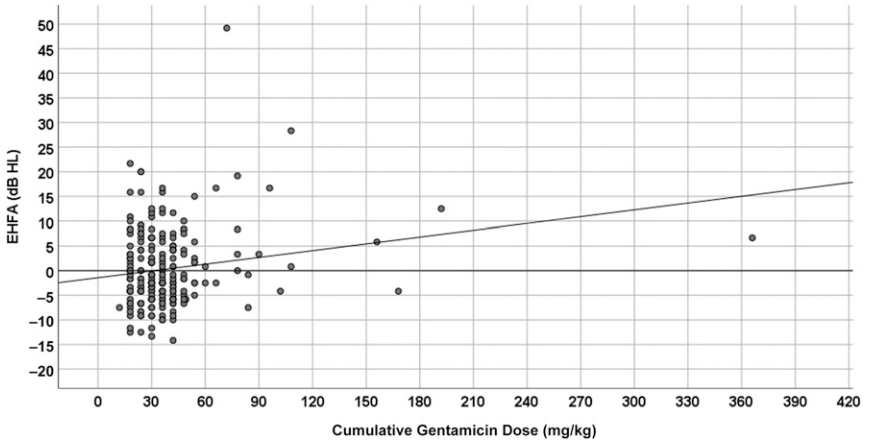
Supplemental Information



SUPPLEMENTAL FIGURE 3
Scatter plot showing the correlation between cumulative gentamicin dose (mg/kg) in all infants and the hearing threshold in the EHFs (9–16 kHz). R^2 linear = 0.033. P = .007 using linear regression statistics; P = .15 using Spearman's nonparametric correlation.

SUPPLEMENTAL TABLE 5 Comparison of GA, Birth Wt, and Gentamicin Exposure in the Original Gentamicin Cohort and Follow-up Cohort 6 to 14 Years Later

	Original Cohort (n = 440)	Follow-up Cohort (n = 219)
GA, wk, median (IQR)	39 (32–40)	39 (33–41)
Birth wt, g, median (IQR)	3281 (1850–3815)	3360 (2154–3896)
<1500, n (%)	84 (19)	39 (18)
Gentamicin TPC, mg/L, median (IQR)	1.0 (0.7–1.3)	1.0 (0.7–1.2)
TPC >2.0, n (%)	26 (6.0)	11 (5.0)
Gentamicin cumulative dose, mg/kg, median (IQR)	30 (24–36)	30 (24–42)

Paper II

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RESEARCH

Hearing impairment after asphyxia and neonatal encephalopathy: a Norwegian population-based study

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Abstract

The purpose of this study is to evaluate the association between perinatal asphyxia, neonatal encephalopathy, and childhood hearing impairment. This is a population-based study including all Norwegian infants born ≥ 36 weeks gestation between 1999 and 2014 and alive at 2 years ($n = 866{,}232$). Data was linked from five national health registries with follow-up through 2019. Perinatal asphyxia was defined as need for neonatal intensive care unit (NICU) admission and an Apgar 5-min score of 4–6 (moderate) or 0–3 (severe). We coined infants with seizures and an Apgar 5-min score < 7 as neonatal encephalopathy with seizures. Infants who received therapeutic hypothermia were considered to have moderate-severe hypoxic-ischemic encephalopathy (HIE). The reference group for comparisons were non-admitted infants with Apgar 5-min score ≥ 7. We used logistic regression models and present data as adjusted odds ratios (aORs) with 95% confidence intervals (CI). The aOR for hearing impairment was increased in all infants admitted to NICU: moderate asphyxia aOR 2.2 (95% CI 1.7–2.9), severe asphyxia aOR 5.2 (95% CI 3.6–7.5), neonatal encephalopathy with seizures aOR 7.0 (95% CI 2.6–19.0), and moderate-severe HIE aOR 10.7 (95% CI 5.3–22.0). However, non-admitted infants with Apgar 5-min scores < 7 did not have increased OR of hearing impairment. The aOR for hearing impairment for individual Apgar 5-min scores in NICU infants increased with decreasing Apgar scores and was 13.6 (95% CI 5.9–31.3) when the score was 0.

Conclusions: An Apgar 5-min score < 7 in combination with NICU admission is an independent risk factor for hearing impairment. Children with moderate-severe HIE had the highest risk for hearing impairment.

What is Known:
- *Perinatal asphyxia and neonatal encephalopathy are associated with an increased risk of hearing impairment.*
- *The strength of the association, and how other co-morbidities affect the risk of hearing impairment, is poorly defined.*

What is New:
- *Among neonates admitted to a neonatal intensive care unit (NICU), decreased Apgar 5-min scores, and increased severity of neonatal encephalopathy, were associated with a gradual rise in risk of hearing impairment.*
- *Neonates with an Apgar 5-min score 7, but without NICU admission, did not have an increased risk of hearing impairment.*

Keywords Apgar score · Neonatal morbidity · Hypoxic-ischemic encephalopathy · Hearing impairment · Sensory loss

Communicated by Daniele De Luca

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Abbreviations

BMI	Body mass index
BW	Birth weight
GA	Gestational age
HIE	Hypoxic-ischemic encephalopathy
MBRN	Medical Birth Registry of Norway
NICU	Neonatal intensive care unit
NPR	Norwegian Patient Registry
SGA	Small for gestational age

Introduction

Childhood hearing impairment is a matter of public health interest because of both high prevalence and the potential negative impact on language and general development if not early and correctly diagnosed and treated [1, 2]. Perinatal asphyxia and neonatal encephalopathy may cause long-term disability among survivors [3–6] and are risk factors for sensorineural hearing impairment [7–9]. The reported risk of later hearing impairment in neonates exposed to asphyxia and neonatal encephalopathy varies between studies [5, 10, 11] and depends on prenatal susceptibility, co-morbidities, and exposures to other potential harmful or protective therapies [8, 9]. Increased understanding of the etiology of childhood hearing impairment is important for preventive measures, prognostic evaluation, and to identify high-risk populations for targeted surveillance [7].

A clinical diagnosis of perinatal asphyxia is optimally based upon documented impaired gas exchange of the fetus[12]. The Apgar score alone is not a diagnostic tool for asphyxia, but the majority of scores less than seven after 5 min may still be attributed to asphyxia, and low Apgar scores are correlated to cord blood gas acidosis [12–14]. In epidemiological studies, a low Apgar score has a high predictive value for later development of cerebral palsy and epilepsy [4, 15, 16]. Population-based studies have also shown an increasing risk of hearing impairment with decreasing Apgar scores, but often without adequate correction for possible confounders [9, 17]. The introduction of therapeutic hypothermia for neonates with moderate-severe neonatal encephalopathy of presumed hypoxic-ischemic origin has reduced mortality and long-term disability in survivors [6, 18]. However, the prevalence of hearing impairment in this population is still high [6, 10, 18, 19], and it is unclear if therapeutic hypothermia can modify this outcome [6, 18]. Contemporary information regarding rates of hearing impairment, risk factors, and associated morbidities among neonates with perinatal asphyxia and neonatal encephalopathy are needed.

In this population-based registry study, we aimed to identify the association between perinatal asphyxia, neonatal encephalopathy, other neonatal morbidities, and sensorineural hearing impairment in an unselected population of all Norwegian infants born ≥ 36 weeks gestation in the 16-year period 1999–2014, and with follow-up data on diagnosed hearing impairment for all participants through 2019.

Methods

Data sources, setting, and study approval

We collected individual-level data on study participants from five Norwegian national health and social registries (Supplementary Table 1). Data were linked using the unique Norwegian 11-digit personal identification numbers of the infant and the mother. The Medical Birth Registry of Norway (MBRN) has almost complete prospectively collected data on pregnancy, delivery, and maternal and neonatal health until 12 months of age [20, 21]. The Norwegian Patient Registry (NPR) contains diagnoses (International Classification of Diseases, 10th Revision-ICD-10) and surgical and medical procedural codes reported from health care providers in both public and private specialist-health care sectors since its inception in 2008 [22, 23]. Reimbursement for inpatient and outpatient visits is based on automatic reports to the NPR, providing a high completeness of data. We included in this study NPR data from 2008 through 2019. The Norwegian National Insurance Scheme (NIS) is the public social security system in Norway with data on diagnoses for illness-related expenses, including people suffering from hearing impairment [24]. Financial compensation is without regard to wealth or income, and virtually everyone with a diagnosis entitled to financial benefit is registered in the NIS. We included data from NIS through 2019. The Norwegian Cause of Death registry contains time and cause of death according to ICD-10 diagnoses [25]. Statistics Norway contains data on parental immigration status and the educational level of the mother.

Universal newborn hearing screening was established in Norway in 2008. 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).

Study population—inclusion and exclusion criteria

Our target population, identified from the MBRN, were infants born ≥ 36 completed weeks gestation in Norway in the 16-year period 1999–2014 (Fig. 1). We excluded children who died during the first 2 years of life due to insufficient follow-up time for hearing impairment diagnosis. We also excluded children with congenital malformations, considered a major confounding factor for the association between asphyxia and hearing impairment [2]. Preterm infants less than 36 weeks gestation

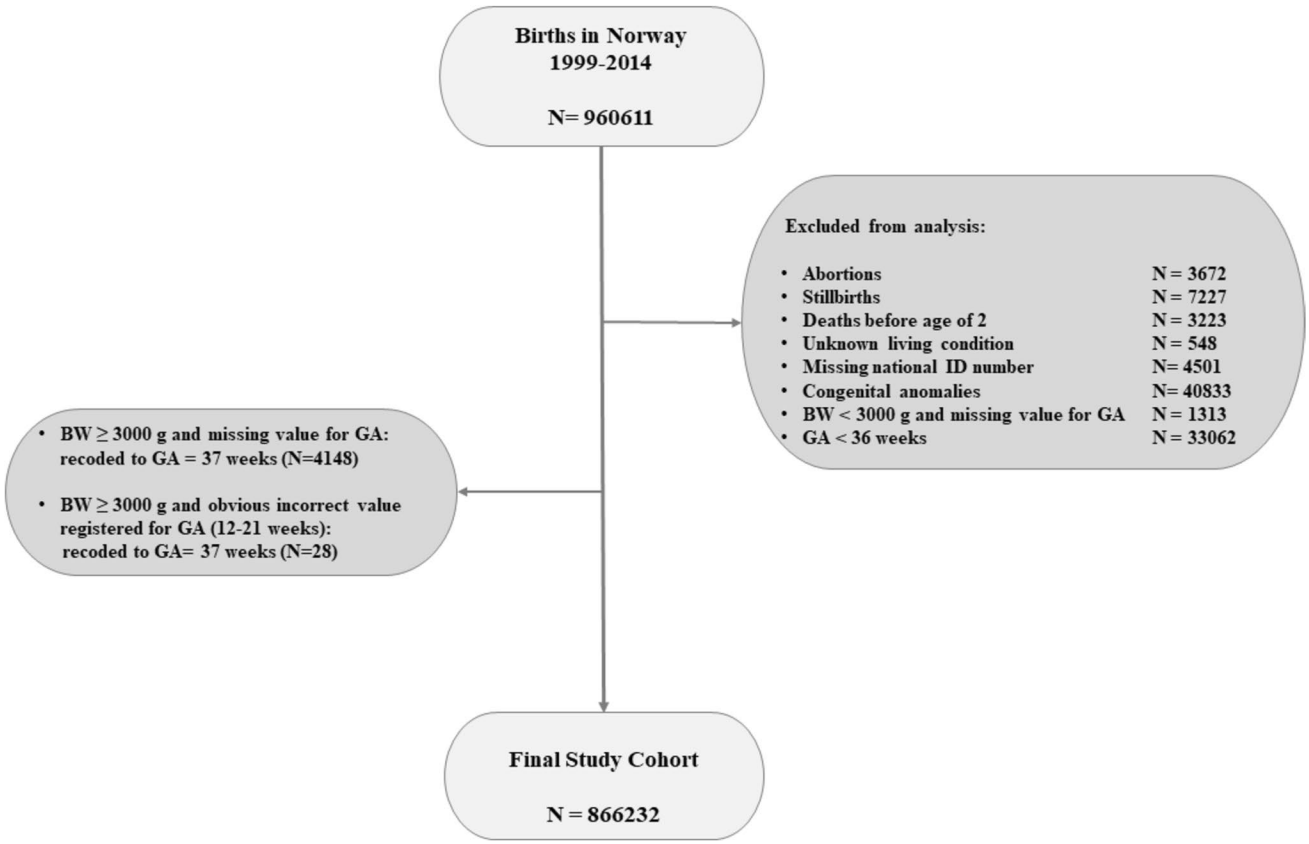


Fig. 1 Study cohort flow diagram. BW birth weight, GA gestational age, ID identification

were excluded to remove the influence of prematurity complications associated with increased rates of hearing impairment [26]. Among children with missing or obviously incorrect data for gestational age (GA) at birth, we included those with birthweight ≥ 3000 g and alive at 2 years of age and pragmatically assigned them a GA of 37 weeks.

Exposures

We defined six different exposure groups and a healthy reference group consisting of non-admitted infants with an Apgar 5-min score ≥ 7 (Table 1). In Norway, cord blood gas analyses are not the routinely taken except in high-risk deliveries, and data were not available from the MBRN.

The main exposure was perinatal asphyxia, defined as the need for neonatal intensive care unit (NICU) admission in combination with an Apgar 5-min score below 7 [27], and further subclassified into a moderate group and a severe group with 5-min scores of 4–6 and 0–3, respectively. We considered the need for NICU admission in these term/near-term infants as a sign of neonatal compromise with symptoms requiring observation and/or therapy. The group of infants with Apgar 5-min scores < 7 and not admitted to a NICU were considered to have had a "rapid recovery" and not classified as perinatal asphyxia. Infants admitted to a NICU with Apgar 5-min scores ≥ 7 were defined in a separate exposure group classified as "other neonatal morbidity." For these four groups, data was available for the entire 16-year cohort.

Neonatal encephalopathy was a secondary exposure and was subclassified in two separate groups. The first group was coined neonatal encephalopathy with seizures and defined as newborn infants admitted to a NICU with an Apgar 5-min score < 7 and diagnosed with neonatal seizures, but not receiving therapeutic hypothermia. The second group was coined moderate-severe HIE and included infants that received therapeutic hypothermia after inclusion criteria specified in the original TOBY study protocol [28]. Data on neonatal encephalopathy was based on diagnoses and therapies registered in the NPR and therefore only available for the 2008–2014 birth cohort.

In addition to analyses of hearing impairment in these six specific exposure groups, we analyzed the association between individual Apgar scores in NICU-admitted children and their subsequent risk of hearing impairment.

Confounders, mediators, and covariates

GA was determined by second-trimester fetal ultrasound and, if missing, by the last menstrual period. Other maternal

Table 1 Infants born ≥ 36 weeks gestation in Norway 1999–2014 and alive at 2 years of age. Distribution of maternal and infant characteristics in groups according to severity of perinatal asphyxia and neonatal encephalopathy and other morbidities

Total cohort ***N*** **= 866,232**	**Reference group** ***N*** **= 759,322**	**Group 1** ***N*** **= 53,572**	**Group 2** ***N*** **= 2175**	**Group 3** ***N*** **= 4591**	**Group 4** ***N*** **= 972**	**Group 5*** ***N*** **= 115**	**Group 6*** ***N*** **= 155**
Criteria for group definition	Apgar 5-min 7–10 No NICU admission	Apgar 5-min 7–10 NICU-admission	Apgar 5-min < 7 No NICU admission	Apgar 5-min 4–6 NICU-admission	Apgar 5-min 0–3 NICU-admission	Apgar 5-min < 7 NICU-admission Seizures, no TH	Received therapeutic hypothermia (TH)
Clinical description	**Healthy**	**Neonatal illness—not asphyxia**	**Low Apgar score, rapid recovery**	**Moderate asphyxia**	**Severe asphyxia**	**Neonatal encephalopathy with seizures**	**Moderate-severe HIE**
Maternal characteristics							
Daily smoking early in pregnancy*	83,906 (13.1)	7426 (16.5)	266 (14.6)	520 (13.8)	104 (13.1)	19 (18.6)	10 (7.2)
Low education (high school or less)	340,518 (44.8)	26,575 (49.6)	1022 (47.0)	2159 (47.0)	489 (50.3)	59 (51.3)	67 (43.2)
Body mass index ≥ 30 **	22,099 (12.0)	2323 (17.4)	78 (14.2)	210 (19.6)	42 (17.4)	9 (20.0)	15 (20.0)
Parental consanguinity	7646 (1.0)	597 (1.1)	36 (1.7)	44 (1.0)	11 (1.1)	1 (0.9)	0
Immigrant	94,186 (12.4)	6633 (12.4)	303 (13.9)	658 (14.3)	141 (14.5)	21 (18.3)	26 (16.8)
Emergency cesarean delivery	57,481 (7.6)	11,089 (20.7)	310 (14.3)	1410 (30.7)	356 (36.6)	36 (31.3)	58 (37.4)
Infant characteristics							
Mean (SD) birth weight (g)	3584 (494)	3472(691)	3611 (567)	3548 (618)	3580 (634)	3568 (593)	3643 (617)
Mean (SD) head circumference (cm)	35 (1.6)	35 (1.9)	35 (1.6)	35.4 (1.8)	35.5 (1.6)	35.4 (1.6)	35.4 (1.5)
Median (IQR) gestational age (weeks)	40 (39–41)	39 (38–40)	40 (39–41)	40 (39–41)	40 (39–41)	40 (39–41)	40 (39–41)
Male	383,553 (50.5)	30,784 (57.5)	1243 (57.1)	2598 (56.6)	536 (55.1)	63 (54.8)	84 (54.2)
Small for gestational age	62,871 (8.3)	8975 (16.8)	257 (11.8)	709 (15.4)	164 (16.9)	22 (19.1%)	21 (13.5)
Jaundice therapy	29,244 (3.9)	10,933 (20.4)	117 (5.4)	404 (8.8)	63 (6.5)	4 (3.5)	3 (1.9)
Antibiotic therapy	NA	13,498 (25.2)	NA	1780 (38.8)	561 (57.7)	93 (80.9)	150 (96.8)
Non-invasive respiratory support	NA	3683 (6.9)	NA	980 (21.3)	251 (25.8)	38 (33)	64 (41.3)
Mechanical ventilation	NA	464 (0.9)	NA	386 (8.4)	319 (32.8)	45 (39.1)	127 (80.9)

Data are number and proportions (%), unless otherwise stated

HIE hypoxic-ischemic encephalopathy, *min* minute, *NA* not applicable, *NICU* neonatal intensive care unit, *TH* therapeutic hypothermia

* Missing data for 15.7% of population; **Missing data for 77% of population; *** Data available for birth cohorts 2008–2014 only (*N* = 391,817)

variables included in the analysis were body mass index (BMI), daily smoking early in pregnancy, immigrant status, parental consanguinity, educational level, and mode of delivery. Neonatal variables, obtained from the MBRN or NPR, were infant sex, birthweight, head circumference, small for gestational age (SGA) defined as birthweight < 10

percentile for GA, antibiotic therapy, neonatal sepsis (ICD-10 code P36 newborn sepsis), jaundice therapy, non-invasive respiratory support, and mechanical ventilation.

Outcomes and definitions

The main outcome of this study, sensorineural hearing impairment, was defined by selected ICD-10 codes for hearing impairment retrieved from two registries (NPR and NIS). From NPR, we included patients registered with the ICD-10 codes H90.3–5 for sensorineural hearing impairment. To reduce false positive cases due to possible coding errors, one of the ICD-10 codes H90.3–5, or a combination of these codes, had to be registered a minimum of two times in the NPR before we considered that the patient had a definite diagnosis of sensorineural hearing impairment. Patients with a diagnosis of conductive, mixed, or unspecified hearing loss registered in the NPR were not included as these are mainly related to middle ear disease, genetic syndromes, or craniofacial deformities and not associated with hypoxic damage to the cochlea or central auditory system, which is the focus of this study. In order to capture cases from two independent registries, we also identified patients with hearing impairment diagnosis from the NIS. As expected, a much lower number of patients were identified in the NIS. Moreover, an explorative analysis of ICD-10 diagnoses in the NIS showed that most codes for hearing impairment were coded as "unspecific," probably reflecting a focus on the degree of disability and not diagnostic code accuracy. From NIS, we therefore added all patients registered with "H90 Conductive and sensorineural hearing loss" and "H91 Other and unspecified hearing loss." A complete list of the ICD-10 diagnoses for hearing impairment and the number of cases included from the NPR and the NIS is displayed in Supplementary Table 2.

Statistical methods

We used the SPSS software (28.0.1.0) for all statistical analyses. Results are presented as proportions, means with standard deviations (SD), or medians with interquartile range (IQR), as appropriate. To evaluate the association between sensorineural hearing impairment and the exposure groups of interest, we used logistic regression analysis with reference to the group of children that had an Apgar 5-min score between 7 and 10 points and no record of a NICU admission. For the analysis of individual Apgar 5-min score values, we used non-admitted children with an Apgar 5-min score equal to 10 as a reference. Based on previous reports [8, 9], and by drawing directed acyclic graphs (DAGs) (Fig. 2), we identified possible confounders as fetal growth restriction and perinatal infection. We found it valid to use the variable SGA as a marker for growth restriction and adjusted for this in our main analysis. Data for antibiotic use (in birth cohorts 1999–2014) and both culture-proven and culture-negative neonatal sepsis (in birth cohorts 2008–2014) were available

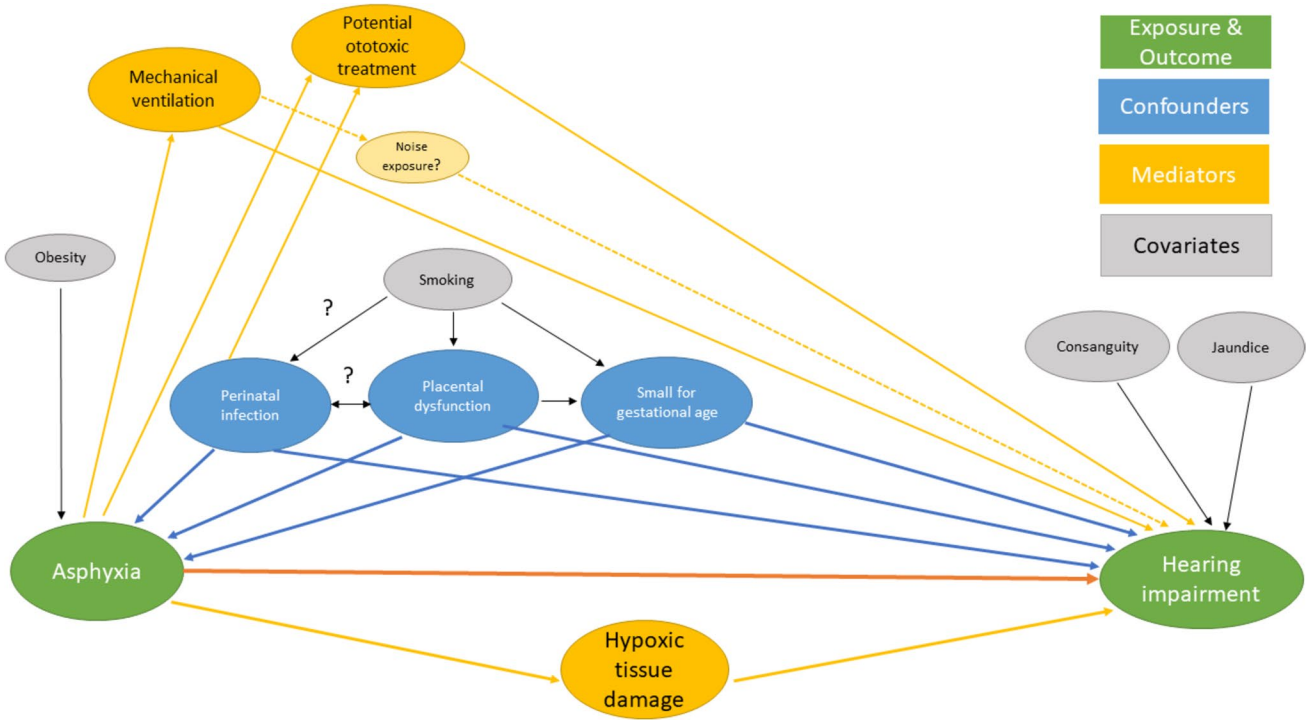
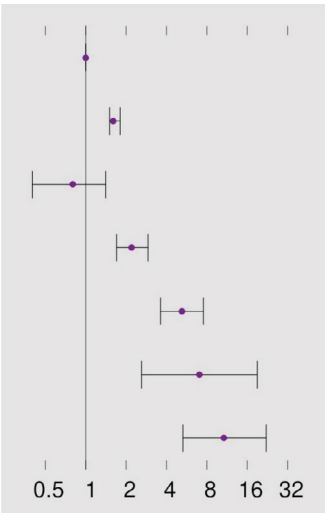


Fig. 2 Directed acyclic graph on associations between perinatal asphyxia and hearing impairment

Table 2 Prevalence, crude, and adjusted odds ratio (OR) for sensorineural hearing impairment, in relation to perinatal asphyxia and neonatal morbidity, among 866,232 infants born ≥ 36 weeks gestation in Norway 1999–2014 and alive at 2 years of age

Clinical description of exposure	Criteria	Hearing impairment N (%)	Crude OR (95 % CI)	Adjusted OR* (95 % CI)
Healthy reference group N=759 322	Apgar 5-min 7-10 No NICU admission	4 488 (0.6)	1.0 (reference)	1.0 (reference)
Neonatal illness - not asphyxia N=53 572	Apgar 5-min 7-10 NICU-admission	521 (1.0)	1.6 (1.5-1.8)	1.6 (1.5-1.8)
Low Apgar score, rapid recovery N=2 175	Apgar 5-min < 7 No NICU admission	10 (0.5)	0.8 (0.4-1.4)	0.8 (0.4-1.4)
Moderate asphyxia N=4 591	Apgar 5-min 4-6 NICU-admission	60 (1.3)	2.1 (1.2-2.7)	2.2 (1.7-2.9)
Severe asphyxia N=972	Apgar 5-min 0-3 NICU-admission	30 (3.1)	5.1 (3.5-7.3)	5.2 (3.6-7.5)
Neonatal encephalopathy with seizures† N=115	Apgar 5-min < 7 Neonatal seizures, no TH NICU-admission	4 (3.5)	7.2 (2.6-19.5)	7.0 (2.6-19.0)
Moderate-severe HIE † N=155	Received TH NICU-admission	8 (5.2)	10.9 (5.3-22.1)	10.7 (5.3-22.0)



HIE hypoxic-ischemic encephalopathy, *min* minute, *NICU* neonatal intensive care unit, *TH* therapeutic hypothermia

* Adjusted for being small for gestational age

[a] Data available only for birth cohorts 2008–2014 ($N = 391,817$)

(Table 1). However, these variables would overestimate the true burden of severe perinatal infection and potentially lead to overcorrection. Thus, we only used them, in addition to SGA, for adjustment in an explorative analysis. The main analysis was repeated with interaction term to investigate possible differences between boys and girls. Crude and adjusted odds ratios (ORs) are presented with a 95% confidence interval (CI).

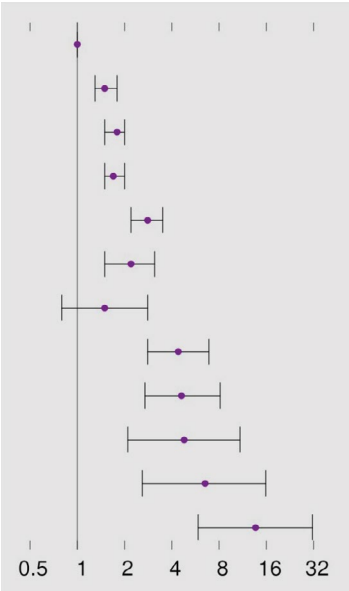
Results

From January 1, 1999, through December 31, 2014, 960,611 births with GA ≥ 36 weeks were registered in Norway. After exclusions, the final study cohort constituted 866,232 children (Fig. 1). Apgar 5-min scores were available for 864,944 (99.9%) of the study participants. Maternal and infant characteristics are displayed in Table 1. In the final study cohort, 7845 (0.9%) of all newborn infants had an Apgar 5-min score < 7, and among these, 5563 (70.9%) infants were admitted to a NICU. Among admitted infants with Apgar 5-min score 0–3 or infants with neonatal encephalopathy, antibiotic therapy and mechanical ventilation were markedly more common than for all other groups. Boys were overrepresented in all groups admitted to a NICU and among non-admitted newborn infants with an Apgar 5-min score < 7.

The prevalence of sensorineural hearing impairment, diagnosed after a minimum 5-year follow-up, in healthy newborn infants with an Apgar 5-min score of 7–10 and not admitted to a NICU ($n = 759,322$) was 0.6%, equal in boys and girls. The prevalence of sensorineural hearing impairment was increased in all infants admitted to a NICU (Table 2), but not significantly different between boys and girls with perinatal asphyxia (Supplementary Table 3). The severity of perinatal asphyxia was associated with a higher prevalence of sensorineural hearing impairment, and it was highest among infants with moderate-severe HIE. However, infants with an Apgar 5-min score < 7, but not admitted to a NICU, did not have an increased prevalence of sensorineural hearing impairment. Results remained similar in exploratory analyses adjusting also for antibiotic therapy/sepsis (Supplementary Table 4). Table 3 displays crude and adjusted ORs for sensorineural hearing impairment for individual Apgar 5-min score values among infants admitted to a NICU, with reference to non-admitted infants with an Apgar 5-min score of 10. The ORs increased markedly with decreasing Apgar 5-min values, and the adjusted OR (aOR) was 13.6 (95% CI 5.9–31.3) in infants with an Apgar 5-min score of 0. We also analyzed the Apgar 5-min scores as a continuous variable, and each unit decrease in the Apgar 5-min score was associated with an aOR of 1.15 (95% CI 1.13–1.17) of sensorineural hearing impairment. In Supplementary Table 5, we present a separate analysis for confounders, covariates, and

Table 3 Apgar 5-min scores, crude, and adjusted odds ratio (OR) for sensorineural hearing impairment among 59,135 infants born ≥ 36 gestation and admitted to NICU in Norway 1999–2014 and alive at 2 years of age

Apgar 5-min	N (%)	Hearing impairment N (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI) **	Adjusted OR (95 %)
Reference *	456 509	2 484 (0.5)	1.0 (reference)	1.0 (reference)	
10	18 530 (31.3)	158 (0.9)	1.6 (1.3-1.8)	1.5 (1.3-1.8)	
9	22 902 (38.7)	226 (1.0)	1.8 (1.6-2.1)	1.8 (1.5-2.0)	
8	7 767 (13.1)	71 (0.9)	1.7 (1.3-2.1)	1.7 (1.5-2.0)	
7	4 373 (7.4)	66 (1.5)	2.8 (2.2-3.6)	2.8 (2.2-3.5)	
6	2 582 (4.4)	31 (1.2)	2.2 (1.6-3.2)	2.2 (1.5-3.1)	
5	1 207 (2.0)	10 (0.8)	1.5 (0.8-2.8)	1.5 (0.8-2.8)	
4	802 (1.4)	19 (2.4)	4.4 (2.8-7.0)	4.4 (2.8-6.9)	
3	513 (0.9)	13 (2.5)	4.8 (2.7-8.3)	4.6 (2.7-8.1)	
2	229 (0.4)	6 (2.6)	4.9 (2.2-11.1)	4.8 (2.1-10.9)	
1	145 (0.2)	5 (3.4)	6.5 (2.7-16.0)	6.5 (2.6-15.8)	
0	85 (0.1)	6 (7.1)	13.9 (6.0-32.0)	13.6 (5.9-31.3)	



NICU neonatal intensive care unit, *min* minute

* The reference was children with Apgar 5-min = 10 and not admitted to a NICU; ** Adjusted for a diagnosis of being small for gestational age

mediators. After adjustment for severe perinatal asphyxia, the variables that remained associated with an increased aOR (95% CI) for sensorineural hearing impairment were neonatal mechanical ventilation 2.9 (1.4–5.9), being SGA 1.3 (1.2–1.4), neonatal jaundice therapy 1.2 (1.1–1.4), parental consanguinity 1.9 (1.5–2.3), daily smoking early in pregnancy 1.3 (1.2–1.5), and maternal low education 1.2 (1.2–1.3).

Discussion

In this population-based study with an unselected cohort of more than 866,000 infants born ≥ 36 weeks gestation, we found that perinatal asphyxia, defined as an Apgar 5-min score < 7 and need for NICU admission, was an independent risk factor for sensorineural hearing impairment. In line with others [17], we observed an inverse relation between the Apgar 5-min scores and the later risk of sensorineural hearing impairment. The highest risk of sensorineural hearing impairment was observed among babies who had moderate-severe HIE. In contrast, we found that Apgar 5-min scores < 7 in infants not admitted to a NICU had no increased risk for sensorineural hearing impairment.

Studies investigating the associations between low Apgar scores and hearing impairment [29] report conflicting results [9, 17, 30–32]. In a study of 11,000 infants, an Apgar 5-min score < 7 was not associated with hearing screening failure at NICU discharge, but the study lacked data on neonatal encephalopathy [30]. In contrast, in a smaller study including only "at risk" infants, an Apgar 5-min score < 7 was a significant risk factor for hearing screening failure, but without adjustments for other risk factors, including prematurity [31]. The inconsistent results are probably due to differences in populations including infants with co-morbidities like prematurity and birth malformations that may affect the predictive value of the Apgar score [15]. Moreover, a newborn hearing screening result does not represent a permanent hearing loss, and delayed onset hearing loss is reported to be more frequent in children exposed to asphyxia or intensive care therapy [7]. A Norwegian study on infants born between 1978 and 1998 found a similar increase in ORs for permanent hearing impairment in relation to low Apgar score as in our study [17]. Another population-based study with a 3-year follow-up of around 115,000 babies found that 8.9% of children with Apgar 5-min score < 7 was later diagnosed with permanent hearing impairment, corresponding to an OR of 20. Notably, half of them were of delayed-onset and diagnosed after the newborn hearing screen [9]. The much higher prevalence and risk for hearing impairment found in this latter study could be explained by also including preterm infants and not adjusting for confounding morbidities.

A salient finding in our study was the lack of association between Apgar 5-min scores < 7 and sensorineural hearing impairment in children with no history of NICU admission. This may have different explanations. Infants not admitted

to a NICU did probably not have other co-morbidities, and several studies indicate that the synergistic effect of several harmful exposures is more important than a low Apgar score alone [9, 17, 30–32]. Also, the inner ear and cochlear structures may be more resilient to hypoxia compared with other parts of the brain. Studies on associations between Apgar 5-min scores and cerebral palsy [4, 16] report much higher ORs for cerebral palsy at the same Apgar 5-min score levels than the ORs for sensorineural hearing impairment in our study, and this may support our theory.

We found a high prevalence of sensorineural hearing impairment (5.2%) in infants who had received therapeutic hypothermia, in line with others reporting prevalences between 3.8 and 10%.[6, 10, 18, 19]. Both a Cochrane review on therapeutic hypothermia [18] and follow-up studies in school age [6, 33] report lower absolute numbers of hearing impairment in cooled infants compared with normothermia, but not reaching significance, which could be due to small samples. Our study was not designed to assess a potential protective effect of cooling for hearing impairment. However, the effect of hypothermia on the inner ear has been thoroughly evaluated in animal studies in which hypothermia had significant and potentially clinically meaningful otoprotection [34].

The precise pathophysiological mechanisms behind hearing impairment caused by perinatal asphyxia and hypoxia remain unclear. Both clinical studies with objective hearing tests [35] and postmortem pathological studies [36] indicate that hypoxia may damage both hair cells of the cochlea and affect retrocochlear auditory function [37]. There is also evidence that synergistic effects between asphyxia and other insults, like jaundice, may play a role in the pathogenesis [38]. A study on cochlear hair cell function in infants exposed to mild and moderate asphyxia found that they had significantly reduced otoacoustic activity in cochlear hair cells compared to controls, even though they had passed the newborn hearing screening [39]. Thus, an early hypoxic event can impose an increased risk for delayed-onset hearing impairment.

Our study adds information for the design of targeted hearing surveillance and intervention programs, based on risk factors for hearing impairment [9]. The Joint Committee of Infant Hearing has regularly updated their risk factors, and therapeutic hypothermia was included in the latest position statement from 2019 [7]. Based on data from our study, an Apgar 5-min score < 4 and admission to a NICU or clinical signs of neonatal encephalopathy are strong risk factors for later hearing impairment. In contrast, a more moderate perinatal asphyxia and/or low Apgar scores alone without the need for NICU admission is not associated with high risk.

The strength of this study is that it includes a large, population-based national cohort. We used data from several validated national registries to identify the vast majority of individuals with hearing impairment and to include relevant confounders. We used DAGs to select confounders for the logistic regression analysis, but cannot exclude residual confounding. If the Apgar 5-min score is < 7, it is recommended that an infant should be observed closely [12]. We therefore added the need for NICU admission in our definition of perinatal asphyxia. Lack of cord blood gas data is a limitation with our study. Still, in other studies, authors have reported consistent associations between low Apgar scores and other adverse neurodevelopmental outcomes [4, 16]. Moreover, cord blood gas acidosis is not a good predictor of perinatal asphyxia [14]. Recent studies from the UK and Sweden reported that Apgar 5-min scores below 7 had a higher predictive value for HIE development than a low pH in the cord blood [40, 41]. Our study could not assess the degree of hearing impairment as the ICD-10 codes for hearing impairment do not include criteria for hearing level in decibel (dB), frequency range, or methods for hearing measurement. The overall prevalence of sensorineural hearing impairment in our study population was somewhat higher than reported from other Scandinavian studies [42, 43]. This may be due to different criteria used for diagnosing sensorineural hearing impairment, and that the use of ICD-10 codes may overestimate cases of hearing impairment. However, this will not affect our calculated ORs for different risk groups. Finally, procedural codes for hearing aids and cochlear implants were unfortunately not available for this study. They would have provided a better definition of severe hearing impairment and its impact on patient lives.

Conclusion

An Apgar 5-min score < 7 in combination with a NICU admission was an independent risk factor for hearing impairment in this unselected cohort of 866,000 children. The risk of hearing impairment increased by lower Apgar scores and was highest in children with moderate-severe HIE. Our study contributes with data on risk factors for hearing impairment that can be used for targeted early hearing surveillance, intervention, and follow-up programs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-023-05321-5.

Authors' contributions D.H. conceptualized and designed the study, carried out 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. D.M. had a central role in acquisition of data, extracted variables for the project, participated in design of the study and writing of the manuscript. B.E. had substantial contributions to the design of the work, participated in analysis of data and writing of the manuscript. C.K. conceptualized and designed the study, coordinated, and supervised data collection, directed 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.

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

Declarations

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).

Consent to participate The study uses anonymized data from Norwegian national registries. According to Norwegian law, this type of study design does not require an informed consent from participants.

Consent for publication The study does not publish any individual data that requires a separate consent.

Competing interests The authors declare no competing interests.

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Supplementary Material

Supplementary Table 1. Description of five Norwegian national health and social registries providing data for this study.

Registries	**Description**	**Main variables used in the study**	**Data available from years**
Medical Birth Registry of Norway	Provides data on pregnancy, delivery, and perinatal period.	Maternal health variables, mode of delivery, gestational age, birth weight, Apgar scores, congenital malformations, admission data and basic treatment variables in the neonatal period, see Table 1.	1999- 2019
The Norwegian Patient Registry	Provides data on diagnostic and surgical and medical procedural codes,	Detailed diagnoses for hearing impairment and other relevant diagnoses and therapies used in the NICU, see Table 1.	2008-2019
The Norwegian National Insurance Scheme	Provides data on diagnoses causing illness-related expenses	Only hearing impairment	1999-2019
Norwegian Cause of Death registry	Provides time and cause of death according to ICD-10 diagnoses	Data was used to filter out participants that died before the age of 2 years.	1999-2019
Statistics Norway	Provides data on a wealth of aspects from national statistics in Norway	Data on parental immigration status and educational level of the mother	1999-2019

Supplementary Table 2. Diagnostic codes for hearing impairment in ICD-10 and included cases from 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 91.0	Ototoxic hearing loss	No	No		
H 91.1	Presbycusis	No	No		
H 91.2	Sudden idiopathic hearing loss	No	No		
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

* if registered two times or more

** if registered once or more

Supplementary Table 3. Prevalence, crude and adjusted odds ratio (OR) for sensorineural hearing impairment, in relation to perinatal asphyxia and neonatal morbidity, among boys and girls in a total cohort of 866 232 infants born ≥ 36 weeks gestation between 1999 and 2014 and alive at 2 years of age.

			BOYS	**GIRLS**	**BOYS (1)**	**GIRLS (0)**	**Interaction term**
Gender distribution within group	**Criteria for group definition**	**Clinical description**	**Hearing impairment N %**	**Hearing impairment N (%)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**
Reference group N=759 322 Boys 50.5% (N= 383 553)	Apgar 5-min 7-10 No NICU-admission	**Healthy**	2301 (0.6)	2187 (0.6)	Not applicable	Not applicable	Not applicable
Group 1 N=53 572 Boys 57.5% (N= 30 784)	Apgar 5-min 7-10 NICU-admission	**Neonatal illness - not asphyxia**	298 (1)	223 (1)	1.6 (1.4-1.8)	1.6 (1.4-1.9)	**1.6 (1.4-1.8)**
Group 2 N=2 175 Boys 57.1 % (N=1 243)	Apgar 5-min < 7 No NICU-admission	**Low Apgar score, rapid recovery**	8 (0.6)	2 (0.2)	1.1 (0.5-2.1)	0.4 (0.1-1.5)	3.0 (0.6-14.2)
Group 3 N=4 591 Boys 56.6 % (N=2 598)	Apgar 5-min: 4-6 NICU-admission	**Moderate asphyxia**	38 (1.5)	22 (1.1)	2.4 (1.7-3.3)	1.9 (1.2-2.9)	1.3 (0.8-2.2)
Group 4 N=972 Boys 55.1 % (N=536)	Apgar 5-min: 0-3 NICU-admission	**Severe asphyxia**	19 (3.5)	11 (2.5)	5.9 (3.7-9.4)	4.3 (2.4-7.9)	1.4 (0.7-3.0)
Group 5† N=115 Boys 54.8 % (N=63)	Apgar 5-min < 7 NICU-admission Seizures, no TH	**Neonatal encephalopathy with seizures†**	3 (4.8)	1 (1.9)	9.1 (2.8-29.1)	4.1 (0.6-29.9)	2.6 (0.3- 25.3)
Group 6† N=155 Boys 54.2 % (N=84)	Moderate-severe HIE NICU-admission TH	**Moderate-severe HIE and TH†**	6 (7.1)	2 (2.8)	14.2 (6.2-32.6)	6.2 (1.5-25.1)	2.6 (0.5-13.5)

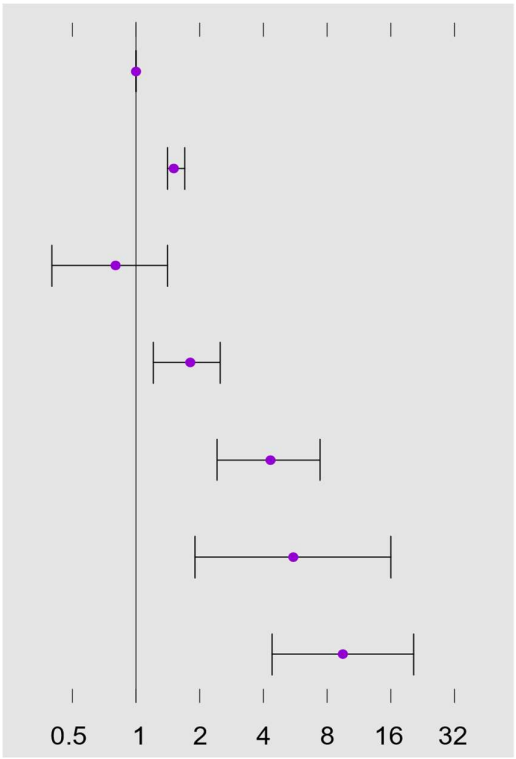
† Data available only for birth cohorts 2008-2014 (N = 391 817)

*Adjusted for a diagnosis of being small for gestational age

HIE; hypoxic-ischemic encephalopathy, NICU; neonatal intensive care unit, TH; therapeutic hypothermia

Supplementary Table 4. Prevalence, crude, and adjusted odds ratio (OR) for sensorineural hearing impairment, in relation to perinatal asphyxia and neonatal morbidity, among 866 232 infants born ≥ 36 weeks gestation in Norway 1999-2014 and alive at two years of age.

Clinical description of exposure	Criteria	Hearing impairment N (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Healthy reference group N=759 322	Apgar 5-min 7-10 No NICU admission	4 488 (0.6)	1.0 (reference)	1.0 (reference)
Neonatal illness - not asphyxia N=53 572	Apgar 5-min 7-10 NICU-admission	521 (1.0)	1.6 (1.5-1.8)	1.5 (1.4-1.7) **
Low Apgar score, rapid recovery N=2 175	Apgar 5-min < 7 No NICU admission	10 (0.5)	0.8 (0.4-1.4)	0.8 (0.4-1.4) **
Moderate asphyxia N=4 591	Apgar 5-min 4-6 NICU-admission	60 (1.3)	2.1 (1.2-2.7)	1.8 (1.2-2.5) **
Severe asphyxia N=972	Apgar 5-min 0-3 NICU-admission	30 (3.1)	5.1 (3.5-7.3)	4.3 (2.4-7.4) **
Neonatal encephalopathy † N=115	Apgar 5-min < 7 Neonatal seizures, no TH NICU-admission	4 (3.5)	7.2 (2.6-19.5)	5.5 (1.9-16.0) ***
Moderate-severe HIE † N=155	Received TH NICU-admission	8 (5.2)	10.9 (5.3-22.1)	9.5 (4.4-20.4) ***



† Data available only for birth cohorts 2008-2014 (N = 391 817)

** Adjusted for neonatal systemic antibiotic therapy and a diagnosis of being small for gestational age

*** Adjusted for being diagnosed with neonatal sepsis and a diagnosis of being small for gestational age

HIE; hypoxic-ischemic encephalopathy, min; minute, NICU; neonatal intensive care unit, TH; therapeutic hypothermia.

Supplementary Table 5. Prevalence, crude, and adjusted odds ratio (OR) for sensorineural hearing impairment in relation to defined confounders, mediators, and covariates among 866 232 infants born ≥ 36 weeks gestation in Norway 1999-2014.

EXPOSURES	N (%)	Hearing impairment N (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI) *
Confounders				
Antibiotic therapy	16 196 (1.9)	200 (1.2)	2.0 (1.8-2.3)	1.4 (0.7-2.7)
Neonatal sepsis †	2 976 (0.8)	38 (1.3)	2.5 (1.8-3.4)	1.7 (0.6-4.8)
Small for gestational age	76 858 (8.9)	645 (0.8)	1.4 (1.3-1.5)	**1.3 (1.2-1.4)**
Mediators				
Mechanical ventilation	1 220 (0.1)	53 (4.3)	7.3 (5.5-9.6)	**2.9 (1.4-5.9)**
Non-invasive respiratory support	5 045 (0.6)	78 (1.5)	2.5 (2.0-3.2)	1.7 (0.8-3.5)
Covariates				
Jaundice therapy	42 555 (4.9)	338 (0.8)	1.3 (1.2-1.4)	**1.2 (1.1-1.4)**
Emergency cesarean delivery	73 860 (8.5)	547 (0.7)	1.2 (1.1-1.3)	1.0 (0.9-1.2)
Maternal obesity** (Body Mass Index ≥ 30)	24 764 (2.9)	136 (0.5)	1.2 (1.0-1.4)	1.1 (0.9-1.4)
Daily smoking early in pregnancy ***	46 529 (5.4)	339 (0.7)	1.4 (1.3-1.5)	**1.4 (1.3-1.5)**
Low education (High school or less)	394 578 (45.6)	2 765 (0.7)	1.2 (1.2-1.3)	**1.2 (1.2-1.3)**
Parental consanguinity	8 970 (1.0)	103 (1.1)	1.9 (1.5-2.3)	**1.9 (1.5-2.3)**

† Data available only for birth cohorts 2008-2014 (N = 391817)

*Adjusted for severe perinatal asphyxia (Apgar 5-min 0-3 and NICU admission)

** Missing data for 77 % of population, not included in analysis. *** Missing data for 15.7 % of population, not included in analysis

Paper III

Hemmingsen, D., Moster, D., Engdahl, B. & Klingenberg, C. (2024).

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

Archives of Disease in Childhood: Fetal and Neonatal Edition.

Appendix

Questionnaire for study cohort Paper I

Langtidsoppfølging av hørsel og nyrefunksjon etter behandling med antibiotika i nyfødtperioden

Spørreskjema om hørsel og nyre/urinveier

(sett kryss for det svaralternativet du mener passer best)

Hørsel

Hvordan oppfatter du ditt barns hørsel?

- Normal
- Lett redusert
- Sterkt redusert
- Bruker høreapparat (hvor gammel var barnet da det fikk høreapparat)

Har ditt barn hatt mye ørebetennelser i barneårene?

- Ja
- Nei

Hvis ja på spørsmål 2; omtrent hvor mange ørebetennelser har ditt barn hatt?

- 1-3
- 4-6
- 7-10
- Flere enn 10

Har ditt barn hatt dren i ørene?

- Ja
- Nei

Er det i familien opphopning av familiemedlemmer som i "ung alder" (før fylte 50 år) har fått behov for høreapparat?

- Nei
- Ja, vennligst beskriv kort:

Er det andre ting vedrørende ditt barns hørsel du vil kommentere?

- Nei
- Ja, vennligst beskriv kort:

Nyre/urinveier

Har ditt barn hatt mange urinveisinfeksjoner i barneårene?

- Ja
- Nei

Hvis ja på spørsmål 2; omtrent hvor mange urinveisinfeksjoner har ditt barn hatt?

- 1-3
- 4-6
- 7-10
- Flere enn 10

Har ditt barn noen kjent nyresykdom?

- Nei
- Ja, vennligst beskriv kort:

Er det i familien opphopning av familiemedlemmer som har nyresykdommer?

- Nei
- Ja, vennligst beskriv kort:

Generelt

Har ditt barn vært innlagt på sykehus og fått antibiotika rett inn i blodåren (intravenøst) etter nyfødtperioden?

- Nei
- Ja, vennligst beskriv kort:

Tusen takk for din deltagelse ☺

Questionnaire for study control group Paper I

Langtidsoppfølging av hørsel og nyrefunksjon etter behandling med antibiotika i nyfødtperioden

Spørreskjema om hørsel

(sett kryss for det svaralternativet du mener passer best)

Barnets navn: ☐

Fødselsdato: ☐

Hørsel

Hvordan oppfatter du ditt barns hørsel?

☐ Normal

☐ Lett redusert

☐ Sterkt redusert

☐ Bruker høreapperat

(hvor gammel var barnet da det fikk høreapperat) ☐

Har ditt barn hatt mye ørebetennelser i barneårene?

☐ Ja

☐ Nei

Hvis ja på spørsmål 2; omtrent hvor mange ørebetennelser har ditt barn hatt?

☐ 1-3

☐ 4-6

☐ 7-10

☐ Flere enn 10

Har ditt barn hatt dren i ørene?

☐ Ja

☐ Nei

Er det i familien opphopning av familiemedlemmer som i "ung alder" (før fylte 50 år) har fått behov for høreapparat?

☐ Nei

☐ Ja, vennligst beskriv kort

Er det andre ting vedrørende ditt barns hørsel du vil kommentere?

☐ Nei

☐ Ja, vennligst beskriv kort

Generelt

Har ditt barn vært innlagt på sykehus og fått antibiotika rett inn i blodåren (intravenøst) etter nyfødtperioden?

☐ Nei

☐ Ja, vennligst beskriv kort

Tusen takk for din deltagelse ☺