Predictors of Cochlear Implantation Outcomes in Children with Auditory Neuropathy Spectrum Disorders

Zahra Jafari

Thesis submitted to the University of Ottawa
in partial fulfillment of the requirements for the
degree of Doctor in Philosophy Rehabilitation Sciences

School of Rehabilitation Sciences
Faculty of Health Sciences
University of Ottawa

General Abstract

Introduction: Auditory neuropathy spectrum disorder (ANSD) is a disorder characterized by impaired temporal coding of acoustic signals due to a deficiency in neural synchrony or neural transmission. Despite variations in speech perception outcomes within both patients and studies, current evidence demonstrates that children with ANSD, who use hearing aids (HAs) or cochlear implants (CIs), generally achieve speech perception performance comparable to peers with sensorineural hearing loss (SNHL). However, limited studies have reported factors that have prognostic value for auditory intervention outcomes. The objectives of this doctoral thesis, consisting of three consecutive associated projects on children with ANSD, were (1) to determine factors with predictive value for post-intervention (CIs and/or HAs) outcomes through a retrospective study, (2) to systematically summarize and critically appraise existing evidence of the prognostic value of early auditory electrophysiologic tests and MRI findings for CI outcomes through a systematic review (SR), and (3) to systematically overview, summarize, and critically appraise evidence of CI outcomes through an umbrella review of current SRs (overview of SRs).

Methods: For the first project, the records of 38 children with ANSD between 5 and 18 years old, 63.20% males, who used CIs (71%) and/or HAs, identified at the Children's Hospital of Eastern Ontario (CHEO) were reviewed. For the second and third projects, the SRs were guided by the PRISMA 2020 statement, and electronic databases were searched without restrictions on language, publication status, or year of publication. In the second project, studies on children with ANSD (including those with cochlear nerve deficiency [CND]), cochleovestibular nerve (CVN) abnormalities, or SNHL reporting the relevance of preoperative and/or postoperative electric compound action potential (eCAP), electric auditory brainstem response (eABR), and/or MRI results to CI outcomes were included. The methodological quality and strength of evidence were

assessed using the Crowe Critical Appraisal Tool (CCAT) and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool, respectively. In the third project, all SRs that reported CI outcomes in children with ANSD were included. The methodological quality of the selected SRs was evaluated using the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) checklist, and the risk of bias in evidence was assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool.

Results: In the retrospective chart review (first project), ages at HL diagnosis and CI activation and the length of follow-up with CI/HA showed a significant relationship with open-set speech perception outcomes (i.e., the scores of Phonetically Balanced Kindergarten [PBK] test with word and phoneme speech materials and Hearing in Noise Test [HINT] in quiet and noise conditions). Using a Forward Linear Multiple Regression Model, the length of follow-up with CI/HA and bilateral amplification showed prognostic value for speech perception performance. In the second project, 25 papers were included in the review. While it was difficult to draw a firm conclusion about the eCAP findings, current evidence strongly supports the prognostic value of eABR and MRI for post-CI speech perception outcomes. According to the eight SRs selected for the third project, children with ANSD achieve CI outcomes comparable to their peers with SNHL. However, in children with postsynaptic ANSD (i.e., those with CND), cochlear nerve hypoplasia is associated with better speech recognition outcomes compared to cochlear nerve aplasia, especially in the absence of additional disabilities and/or medical comorbidities (ADs/MCs).

Conclusion: Children with ANSD, especially those without cochlear nerve aplasia and ADs/MCs, achieve speech perception outcomes comparable to their peers with SNHL. In addition, age at HL diagnosis, age at CI activation, the length of follow-up with CI/HA, bilateral amplification, and eABR and MRI findings are associated with or have predictive value for intervention outcomes.

The findings of the SRs should be interpreted with caution given the low quality of evidence and risk of bias in the studies selected for SRs.

Keywords: Auditory neuropathy spectrum disorder; Cochlear nerve deficiency; Cochlear implant; Hearing aid; Speech perception; Follow-up period; Electric compound action potential; Electric auditory brainstem response; Magnetic resonance imaging; Prognostic value; Predictor; Outcome.

Résumé Général

Introduction: Le trouble du spectre de la neuropathie auditive (TSNA) est un trouble caractérisé par une détérioration de l'encodage temporel des signaux acoustiques en raison d'une dégradation de la synchronisation ou de la transmission neurale. Malgré une variation dans les résultats aux tests de perception de la parole chez les patients et dans les études, les données actuelles démontrent que les enfants atteints du TSNA avec une perte auditive permanente (PA), qui utilisent des aides auditives (AAs) ou des implants cochléaires (ICs), atteignent généralement des performances de perception de la parole comparables à celles de leurs pairs atteints de perte auditive neurosensorielle (PAN). Cependant, parmi un ensemble de facteurs potentiels, peu d'études ont rapporté des facteurs ayant une valeur pronostique pour les résultats de l'intervention auditive. Les objectifs de cette thèse de doctorat, composée de trois projets associés consécutifs sur des enfants atteints de TSNA, étaient (1) de déterminer les facteurs ayant une valeur prédictive pour les résultats post-intervention (ICs ou AAs) par le biais d'une étude rétrospective, (2) résumer systématiquement et évaluer de manière critique les preuves existantes de la valeur pronostique des évalauations électrophysiologiques auditves précoces et des conclusions de l'IRM pour les résultats de l'IC par le biais d'une revue systématique (RS), et (3) passer systématiquement en revue, résumer et évaluer de manière critique les RS actuelles sur les résultats de l'IC par le biais d'une revue générale (vue d'ensemble des RS).

Méthodes: Pour le premier projet, les dossiers de 38 enfants atteints de TSAA âgés de 5 à 18 ans, 63,20 % de sexe masculin, qui utilisaient des IC (71 %) et/ou des AH, identifiés au Centre hospitalier pour enfants de l'est de l'Ontario (CHEO), ont été examinés. Pour les deuxième et troisième projets, les RS ont été guidées par les lignes directrices PRISMA établies en 2020, et les bases de données électroniques ont été consultées sans restriction de langue, de statut de

publication ou d'année de publication. Dans le cadre du deuxième projet, les études portant sur des enfants atteints de TSNA (y compris ceux présentant une déficience du nerf cochléaire [DNC]), d'anomalies du nerf cochléo-vestibulaire (NCV) ou de PAN et faisant état de la pertinence des résultats préopératoires et/ou postopératoires du potentiel d'action électrique composé (eCAP), des potentiels évoqués auditifs électriques du tronc cérébral (PÉATC-e) ou de l'IRM par rapport aux résultats de l'IC ont été prises en compte. La qualité méthodologique et la puissance des données probantes ont été évaluées à l'aide de l'outil Crowe Critical Appraisal Tool (CCAT) et de l'outil Grading of Recommendations, Assessment, Development and Evaluation (GRADE), respectivement. Dans le cadre du troisième projet, tous les rapports de synthèse faisant état de résultats en matière d'IC chez les enfants atteints de troubles du spectre des neuropathies auditives ont été inclus. La qualité méthodologique des RS sélectionnées a été évaluée à l'aide de la liste de contrôle AMSTAR-2 (Assessment of Multiple Systematic Reviews 2), et le risque de biais dans les données probantes a été évalué à l'aide de l'outil ROBIS (Risk of Bias in Systematic Reviews).

Résultats: Dans l'examen rétrospectif des dossiers (premier projet), l'âge au moment du diagnostic de la perte auditive et de l'activation de l'IC, ainsi que la durée du suivi de l'IC/AA, ont montré une relation significative avec les résultats de la perception de la parole choix ouvert (c.-à-d. les résultats du test PBK (Phonetically Balanced Kindergarten) avec les mots et phonèmes et du test HINT (Hearing in Noise Test) dans les conditions de silence et de bruit). En utilisant un modèle de régression linéaire multiple par étapes, la durée du suivi de l'IC/AA et de l'amplification bilatérale a démontré une valeur pronostique pour la performance de la perception de la parole. Dans le cadre du deuxième projet, 25 articles ont été sélectionnés pour être examinés. Bien qu'il ait été difficile de tirer une conclusion ferme sur les résultats de l'eCAP, les données probantes actuelles soutiennent fortement la valeur pronostique des PÉATC-e et de l'IRM pour les résultats

de la perception de la parole post implantation (IC). D'après les huit RS sélectionnés pour le troisième projet, les enfants atteints de TSNA obtiennent des résultats en matière d'IC équivalents à ceux de leurs pairs atteints de PAN. Cependant, chez les enfants souffrant d'un TSNA postsynaptique (Majoritairement de DNC), l'hypoplasie du nerf cochléaire est associée à de meilleurs résultats en matière de reconnaissance de la parole que l'aplasie du nerf cochléaire, en particulier en l'absence de handicaps supplémentaires ou de comorbidités médicales (HSs/CMs).

Conclusion: Les enfants atteints de TSNA, en particulier ceux qui n'ont pas d'aplasie du nerf cochléaire et de HSs/CMs, obtiennent des résultats en matière de perception de la parole équivalents à ceux de leurs pairs atteints de PAN. De plus, l'âge au moment du diagnostic de la perte auditive, l'âge au moment de l'activation de l'IC, la durée du suivi avec l'IC/AA, l'amplification bilatérale et les résultats des PÉATC-e et de l'IRM sont associés aux résultats de l'intervention ou ont une valeur prédictive à cet égard. Les résultats des RS doivent être interprétés avec prudence, compte tenu de la faible qualité des données probantes et du risque de biais dans les études sélectionnées pour les RS.

Mots-clés: Trouble du spectre de la neuropathie auditive; Déficience du nerf cochléaire; Implant cochléaire; Aide auditive; Perception de la parole; Période de suivi; Potentiels d'action électriques composés; Potentiels évoqués auditifs électriques du tronc cérébral; Imagerie par résonance magnétique; Valeur pronostique; Prédicteur; Résultat.

Acknowledgments

I would first like to acknowledge that my doctoral studies were conducted on the traditional and unceded territory of the Anishinaabeg Algonquin People who have inhabited and cared for these lands from time immemorial. As a white, cisgender, heterosexual, and able-bodied settler, I have been afforded many unearned benefits while living, studying, and working on indigenous land.

I would like to express my deepest gratitude to my thesis supervisor, Dr. Amineh Koravand, for her dedication and unwavering support, and enthusiasm; even and especially in the face of change. I am grateful for your mentorship throughout this journey.

I greatly appreciate my thesis advisory committee, Dr. Elizabeth Fitzpatrick, Dr. Isabelle Rouillon, and Dr. David Schramm for their helpful feedback and suggestions throughout the dissertation process; and Dr. Karen Gordon from the University of Toronto for acting as my external examiner. I am grateful for your thoughtful feedback and insight into my dissertation.

I would like to extend my sincere thanks to Dr. Chantal Lessard (Coordinator and Professional Practice Leader at Children's Hospital of Eastern Ontario, CHEO) and JoAnne Whittingham (Research Coordinator at CHEO) for their help and guidance on CHEO's REB Ethical approval and access to patients' records for chart review, and the Office of Research Ethics and Integrity, University of Ottawa, for Letter of Administrative approval.

I am grateful to Ines Telmat and Jennifer Ti Nguyen, two graduate students, for their excellent support with chart review and data extraction.

Funding support from the Ontario Graduate Scholarship (OGS) and the Queen Elizabeth II Scholarships in Science and Technology (QEII-GSST) was offered for my doctoral thesis, for which I am privileged and grateful.

Lastly, this academic endeavor would not have been possible without the unconditional support and encouragement of my family. Thank you to my loving family for their endless support, encouragement, and love. Thank you for brightening my life and celebrating every milestone and accomplishment of my academic career with me.

Content of Dissertation and Contribution Statement

This thesis contains three projects. All three studies were prepared in collaboration with Dr. Amineh Koravand, my doctoral supervisor. Data for the first project were collected at CHEO with ethics approval from both the Children's Hospital of Eastern Ontario (CHEO) and the University of Ottawa Office of Research Ethics and Integrity. Ms. Chantal Lessard and JoAnne Whittingham at CHEO assisted with REB Ethical approval and access to patients' records for chart review. Two graduate students, Ines Telmat and Jennifer Ti Nguyen, helped with chart review and data extraction. I was responsible for preparing and submitting the protocol to the research ethics board, formulating the hypotheses, conducting the literature review, chart review and data management, data analyses, data interpretation, and writing all components of the project.

My second and third studies were two comprehensive systematic reviews (SRs) of existing evidence focused on my doctoral thesis topic. I was responsible for conceptualization, formulating the research questions, preparing and submitting the SR protocols to PROSPERO, conducting a systematic literature search, data extraction, data appraisal, data synthesis, data interpretation, drawing figures, tabulating the data extracted, and writing all components of the projects. My supervisor was one of the reviewers for the systematic search and data extraction for the two SRs, and I regularly consulted with Dr. Koravand on all components of the studies.

Dr. Elizabeth Fitzpatrick, Dr. Isabelle Rouillon, Dr. David Schramm, and my supervisor (co-authors) reviewed the three articles of my doctoral thesis and shared feedback and comments. I was responsible for writing the first draft of the three manuscripts, following up on feedback from the co-authors, revising and preparing the manuscripts for submission, and submitting the manuscripts for publication in peer-reviewed journals with ongoing input from the co-authors.

Table of Contents

Table of Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Table of Figures

Chapter 2

Chapter 3

Chapter 4

List of Acronyms

ABI	Auditory brainstem implant
ABR	Auditory brainstem response
ADs/MCs	Additional disabilities/medical comorbidities
AMSTAR-2	Assessment of Multiple Systematic Reviews 2
AN	Auditory neuropathy
ANRT	Auditory nerve response telemetry
ANSD	Auditory neuropathy spectrum disorders
BKB	Bamford-Kowal-Bench
CAEP	Cortical auditory evoked potential
CAP	Compound action potentials
CAP	Categories of Auditory Performance
CCAT	Crowe Critical Appraisal Tool
CDT	Connected Discourse Tracking
CHEO	Children's Hospital of Eastern Ontario
CI	Cochlear implant
CL	Critically low
CM	Cochlear microphonic
CN	Cochlear nerve
CNC	Consonant-Nucleus-Consonant
CNC	Cochlear nerve canal
CND	Cochlear nerve deficiency
CNS	Central nervous system

CPA	Cerebellopontine angle
CVN	Cochleovestibular nerve
DR	Dynamic range
eABR	electric auditory brainstem response
eCAP	electric compound action potential
EHDI	Early hearing detection and intervention
ENI	Electrode-neuron interface
EPSP	Excitatory postsynaptic potential
ESP	Early speech perception
FDA	Food and Drug Administration
FM	Frequency modulation
FN	Facial nerve
GASP	Glendonald Auditory Screening Procedure
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HA	Hearing aid
HINT	Hearing in Noise Test
HL	Hearing loss
IAC	Internal auditory canal
IHCs	Inner hair cells
IP-EVA	Incomplete partition-enlarged vestibular aqueduct
IT-MAIS	Infant-toddler meaningful auditory integration scale
JCIH	Joint Committee on Infant Hearing
LNT	Lexical neighborhood test
MAIS	Meaningful Auditory Integration Scale

MLNT	Multi-syllable Lexical Neighborhood Test
MRI	Magnetic resonance imaging
MWT	Mono-syllabic Word Test
NICU	Neonatal intensive care unit
NRI	Neural response imaging
NRT	Neural response telemetry
OAEs	Otoacoustic emissions
OCEBM	Oxford Centre for Evidence-Based Medicine
OHCs	Outer hair cells
PB	Preterm birth
PBK-P/W	Phonetically Balanced Kindergarten with phoneme or word stimuli
PICOS	Participants, interventions, comparators, outcomes, and study designs
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
ROBIS	Risk of Bias in Systematic Reviews
SAT	Speech awareness thresholds
SD	Standard deviation
SIR	Speech Intelligibility Rating
SMD	Standard mean difference
SNR	Signal-to-noise ratio
SR	Systematic review
SNHL	Sensorineural hearing loss
tNRT	Predicted neural response telemetry
WIPI	Word Intelligibility by Picture Identification

Chapter 1

General Introduction

Auditory neuropathy (AN) is a disorder characterized by impaired temporal encoding of acoustic signals due to dysfunction in the peripheral auditory system with consequent reduction of auditory perception (Santarelli et al., 2021). Over time, the term AN has changed to auditory neuropathy/dyssynchrony (Berlin et al., 2003) and then auditory neuropathy spectrum disorders (ANSD) (Hayes and Sininger, 2008) to encompass variations in auditory findings, resulting from variations in medical findings, etiologies, or involved anatomic sites (Hall, 2015). Although exact statistics are not yet available, ANSD is rare in the well-baby population, with no more than three per 10,000 births (Bielecki et al., 2012; Hall, 2015; Korver et al., 2012; Rance and Starr, 2011; Starr and Rance, 2015). ANSD is seen in 40% of children with a history of neonatal intensive care unit (NICU) admission (Rea and Gibson, 2003), and genetic disorders play a significant role in ANSD pathogenesis, with nearly one-half of all children with ANSD falling into this group (Gardner-Berry et al., 2019; Hall, 2015; Madden et al., 2002; Manchaiah et al., 2011). Also, ANSD accounts for 4% to 5% of all children with permanent hearing loss (HL), and 10% to 15% of school-age children with severe to profound sensorineural hearing loss (SNHL) (Bielecki et al., 2012; Mittal et al., 2012).

Two basic mechanisms are involved in the disruption of neural activity in ANSD at the auditory brainstem level: (1) “deficiency in neural transmission” or reduced number of activated auditory nerve fibers or deafferentation and (2) “deficiency in neural synchrony or dyssynchrony” (Berlin et al., 2003; Chaudhry et al., 2020; Rance and Starr, 2015; Starr et al., 1996). Based on the anatomic locus of dysfunction and audiologic, electrophysiologic, and genetic findings, ANSD is broadly classified into “presynaptic and postsynaptic disorders”. In presynaptic ANSD (auditory synaptopathy or auditory dyssynchrony) such as otoferlin mutations, the disease involves inner hair cells (IHCs) or ribbon synapses. In postsynaptic ANSD, dysfunction can occur at multiple sites along the auditory nerve pathway, including unmyelinated auditory nerve dendrites or auditory ganglion cells and their myelinated axons and dendrites. While demyelination leads to dysfunction in conduction velocity causing dyssynchrony (i.e., deficiency in neural synchrony), axonal degeneration results in reduced auditory input to the brainstem (i.e., deficiency in neural transmission). In central ANSD, the lesion site is located at the brainstem level, including cerebellopontine angle tumors, such as vestibular schwannomas and meningiomas (Chaudhry et al., 2020; Hall, 2015; Rance and Starr, 2015; Shearer and Hansen, 2019). The involvement of each of these anatomic sites or a combination of them can lead to deficits in neural synchrony and/or neural transmission and severely affect auditory temporal processing (He et al., 2015; Rance et al., 2004; Santarelli et al., 2021).

ANSD has a heterogeneous clinical profile, encompassing a wide range of acquired, genetic (syndromic/non-syndromic), and congenital etiologies (Manchaiah et al., 2011). Various risk factors or diseases may contribute to ANSD, such as perinatal and neonatal factors (e.g., hypoxia, hyperbilirubinemia, and ototoxic drug exposure), genetic and hereditary etiologies, demyelinating diseases, and neurodegenerative disorders (Chaudhry et al., 2020; Hall, 2015;

Rance and Starr, 2015). Approximately 27% to 33% of children with ANSD show evidence of cochlear nerve deficiency (CND) (e.g., due to CHARGE or Waardenburg syndrome) (Holcomb et al., 2013; Huang et al., 2012). CND is characterized by a very abnormal auditory nerve structure, including a small (hypoplastic) or absent (aplastic) cochlear nerve as revealed by high-resolution magnetic resonance imaging (MRI) (Hall, 2015; Roche et al., 2010). In addition, 30% of children with ANSD demonstrate at least one additional disability other than HL (Ching et al., 2013a; Hall, 2015).

Regarding pathogenic mechanisms of ANSD, while non-syndromic auditory neuropathies primarily impact the auditory nerve, syndromic auditory neuropathy involves multiple cranial and peripheral nerves. The primary cause of non-syndromic auditory neuropathy is compromised synaptic transmission (Saidia et al., 2023). Various genes have been implicated in causing non-syndromic auditory neuropathy, leading to what is referred to as genetic auditory synaptopathy (Moser and Starr, 2016). These genetic abnormalities result in specific forms of auditory neuropathy with distinct mechanisms (Moser and Starr, 2016; Saidia et al., 2023):

- Otoferlin-DFNB9: Mutations in the OTOF gene, which encodes otoferlin, lead to autosomal recessive profound prelingual deafness. Otoferlin plays a crucial role in calcium-triggered synaptic exocytosis in inner hair cells (IHCs). Variants in the OTOF gene cause defects in neurotransmitter release and auditory signal transduction (Petersen and Willems, 2006).
- VGLUT3-DFNA25: Genetic mutations affecting the SLC17A8 gene, which encodes vesicular glutamate transporter 3 (VGLUT3), result in non-syndromic autosomal dominant deafness. VGLUT3 is responsible for loading glutamate into synaptic vesicles, and mutations lead to failure in activating the auditory pathway, despite normal outer hair cell (OHC) activity (Ruel et al., 2008).

- Cav1.3-SANDD: Mutations in the CACNA1D gene, responsible for encoding the Cav1.3 L-type calcium channel, cause sensory and neurological disorders including deafness. Cav1.3 channels are essential for sound-evoked neurotransmitter release at the IHC synapse (Shearer and Hansen, 2019).
- CABP2-DFNB93: Calcium-binding protein 2 (CABP2) modulates calcium channels in IHCs. Mutations in the CABP2 gene lead to autosomal-recessive non-syndromic hearing impairment. The impaired synaptic transmission is attributed to altered calcium influx at the IHC synapse (Shearer and Hansen, 2019).
- DIAPH3-AUNA1: Auditory neuropathy, non-syndromic, autosomal dominant 1 (AUNA1) results from a point mutation in the DIAPH3 gene. This mutation causes overexpression of the DIAPH3 protein, leading to progressive hearing loss due to the alteration of the assembly and maintenance of actin filaments in IHC stereocilia (Surel et al., 2016).

Syndromic auditory neuropathies are associated with other neurological conditions and often affect multiple neural systems (Manchaiah et al., 2011; Saidia et al., 2023):

- Charcot–Marie–Tooth: Autosomal-dominant Charcot–Marie–Tooth is a hereditary peripheral polyneuropathy with hearing impairment as a symptom. Demyelinating neuropathies (CMT Type 1) display altered ABRs and speech perception, suggesting defective cochlear neurotransmission (Rance et al., 2012b).
- Autosomal-Dominant Optic Atrophy (DOA): DOA, characterized by optic nerve degeneration, also features hearing loss in some cases. The OPA1 gene, associated with DOA, has variants related to hearing impairment. Auditory neuropathy may underlie hearing issues in DOA (Maeda-Katahira et al., 2019).

- Leber Hereditary Optic Neuropathy (LHON): LHON, a mitochondrial genetic disease, primarily affects vision. However, auditory neuropathy is also observed in patients (Ceranić and Luxon, 2004).
- Friedreich's Ataxia: Friedreich's ataxia, involving a mutation in the FXN gene, leads to both impaired movement coordination and hearing impairment, particularly affecting auditory neural responses (Rance et al., 2012a).
- Mohr–Tranebjaerg Syndrome: This syndrome involves progressive dystonia, visual impairment, and deafness. Neuronal loss with preserved outer hair cells (OHCs) is noted, and mutations in the TIMM8A/DDP1 gene are responsible (Wang et al., 2019).

ANSD is characterized by inconsistency in audiologic results. In behavioral audiometry, hearing thresholds may vary from levels within normal limits to severe to profound SNHL (Sininger and Oba, 2001). While no specific audiogram shape is common (except for low tone loss and flat audiograms in adults), poor speech perception performance, especially in the presence of background noise, is frequent (Madden et al., 2002; Sininger and Oba, 2001; Starr et al., 1996). In addition, audiometric results might be unreliable in some patients, showing fluctuations over time (Madden et al., 2002). In auditory electrophysiological assessments, severely abnormal or no detectable compound action potentials (CAP) and auditory brainstem responses (ABR) are expected. However, individuals with ANSD show normal otoacoustic emissions (OAEs) and robust cochlear microphonic (CM) responses, which are inconsistent with typical cochlear (sensory) HL or are evidence of normal outer hair cell (OHC) function (Madden et al., 2002; Sininger and Oba, 2001; Starr et al., 1991; Starr et al., 1996; Starr and Rance, 2015).

Hearing aids (HAs) are extensively prescribed for people with permanent SNHL to compensate for reduced hearing thresholds. Cochlear implants (CIs) are often recommended for

individuals with severe and profound SNHL and are characterized as a common hearing intervention for children with ANSD, irrespective of HL severity. Overall, CIs are an effective form of remediation for children with ANSD (Walker et al., 2016), and may function better than HAs in speech sound transmission supporting the formation of fundamental aspects of spoken language and verbal communication (Myers and Nicholson, 2021).

Theoretical/Conceptual Framework

According to existing evidence, children with ANSD with different degrees of permanent HL who use HAs or CIs may attain speech perception outcomes equivalent to their peers with SNHL (Bo et al., 2022; Ching et al., 2018; Fernandes et al., 2015; Gardner-Berry et al., 2019; Humphriss et al., 2013; Myers and Nicholson, 2021). However, amplification outcomes show considerable variability within both patients and studies (Bo et al., 2022; Cupples et al., 2018; Myers and Nicholson, 2021; Peng et al., 2017; Rajput et al., 2019; Rance and Starr, 2015; Vesseur et al., 2018). This heterogeneity/inconsistency largely results from diversity in the lesion site and multiple demographic, auditory, and medical factors contributing to outcomes such as additional disabilities and/or medical comorbidities (ADs/MCs), age at HA fitting, age at CI activation, bilateral amplification, the length of follow-up with CI/HA, cognitive function, socioeconomic status, sex, and maternal education (Bo et al., 2022; Ching et al., 2013c; Hall, 2015; Myers and Nicholson, 2021; Starr and Rance, 2015). In addition, sample size (higher likelihood of overestimating intervention effect in studies with low sample sizes) (Dechartres et al., 2013; Zhang et al., 2013), study design (the risk of selection bias in non-randomized studies) (Sterne et al., 2022), and diversity in outcome measures (i.e., a variety of behavioral and/or electrophysiological assessments) (Bo et al., 2022; Myers and Nicholson, 2021; Peng et al., 2017; Vesseur et al., 2018)

are among known factors contributing to inconsistency in existing evidence. Similar to children with SNHL, better outcomes in ANSD are associated with receiving hearing interventions before three years of age (Ching et al., 2013a; Ching et al., 2013b; Niparko et al., 2010). Although there is existing evidence for the benefits of HAs and CIs for children with ANSD (Bo et al., 2022; Myers and Nicholson, 2021; Peng et al., 2017; Vesseur et al., 2018), studies on factors with prognostic value for intervention outcomes are limited.

Among diverse contributing factors to heterogeneity in patients and inconsistency in the literature (Bo et al., 2022; Cupples et al., 2018; Myers and Nicholson, 2021; Peng et al., 2017; Rajput et al., 2019; Rance and Starr, 2015; Vesseur et al., 2018), the lesion site plays a prominent role in ANSD (Bo et al., 2022; Ching et al., 2013a; Hall, 2015; Myers and Nicholson, 2021; Starr and Rance, 2015). For this reason, high-resolution MRI is considered the gold standard in identifying evidence of CND. In addition, both intraoperative and postoperative electric compound action potential (eCAP) and electrically evoked auditory brainstem response (eABR) are commonly used to determine the excitability of the cochlear nerve (CN) and may have predictive value for functional outcomes of electric amplification (Nada et al., 2022; Trecca et al., 2020). While the results of several studies in children account for the prognostic value of MRI (Jeong and Kim, 2013; Kari et al., 2022) and intraoperative and/or postoperative electrophysiologic results (Dutt et al., 2021; Gibson et al., 2009; Yamazaki et al., 2015) for CI outcomes, some studies do not support this finding (Chao et al., 2016; Nikolopoulos et al., 2000). Overall, given the diversity of findings, it is unclear where the body of research stands, what the limitations and perspective of future research are, and how existing evidence can help clinicians with decision-making and counseling parents about CI candidacy.

During the past decade, several systematic reviews (SRs) were published on CI outcomes in children with presynaptic and/or postsynaptic ANSD (Bo et al., 2022; Humphriss et al., 2013; Myers and Nicholson, 2021; Peng et al., 2017; Rance and Starr, 2015; Vesseur et al., 2018). However, current evidence demonstrates a range of CI outcomes in children with ANSD from no significant difference relative to peers with SNHL (Bo et al., 2022) to poor auditory performance in a fraction of children with postsynaptic involvement or evidence of CND (Gibson and Sanli, 2007; Roush et al., 2011; Teagle et al., 2010). In general, given the breadth of findings, it is difficult to draw firm conclusions regarding the CI benefits for children with ANSD, the limitations of existing evidence, future research directions, and the use of current knowledge in decision-making and counseling with parents about CI candidacy.

Based on current evidence, the framework of this doctoral thesis was outlined to research and systematically review the factors that have predictive value for CI outcomes, summarize research limitations, and identify areas for future research. This doctoral thesis on "cochlear implantation outcomes in children with ANSD" aims to:

1. To characterize factors with prognostic value for post-intervention outcomes.
2. To systematically summarize and critically appraise current evidence on the prognostic value of early auditory electrophysiologic tests (i.e., intraoperative and/or postoperative eCAP, and eABR) and MRI findings for post-implantation speech perception outcomes in children with ANSD.
3. To systematically summarize and critically appraise current SRs of CI outcomes in children with ANSD and clarify directions for future research.

In alignment with these three objectives, we hypothesize that:

1. The length of follow-up with CI/HA, age at CI activation, ADs/MCs, and using two CIs/HAs contribute to post-intervention outcomes (the first objective and hypothesis were covered in the first project/publication).
2. Combined electrophysiologic and MRI findings have predictive value for CI outcomes (the second objective and hypothesis were covered in the second project/publication).
3. Most children with ANSD can benefit from CIs, especially children with presynaptic ANSD, without ADs/MCs (the third objective and hypothesis were covered in the third project/publication).

Summary Review of the Literature

Behavioral Predictors of CI Outcomes

Despite several studies on CI outcomes in children with ANSD, studies on factors that have prognostic value for CI outcomes are limited. Table 1 summarizes the findings of two studies on predictors of post-CI speech perception outcomes and indicates the diversity of predictors among studies.

In a prospective study of 451 children with HAs (70%) or CIs (30%) in Australia (i.e., the Longitudinal Outcomes of Children with Hearing Impairment [LOCHI] study), of whom 47 (10%) had ANSD, predictors of intervention outcomes were investigated for children with permanent HL who received hearing services before three years of age (Ching et al., 2013b). In this study, female sex, higher maternal education, and lower age at CI activation were positively associated; and the

presence of ADs was negatively associated with better three-year outcomes. In addition, there was no difference in the factors that predicted better outcomes in children with ANSD and those with SNHL (Ching et al., 2013b). In a similar study in South Africa, predictors of CI outcomes were investigated in 301 children from five CI programs with a minimum of six months of CI use (le Roux et al., 2016). Among contributing factors, the use of two CIs was a strong predictor for better auditory performance and speech production scores, oral mode of communication, and mainstream education. NICU admission and prematurity were associated with lower auditory performance and speech production scores, and a higher probability of non-oral communication and non-mainstream education. The presence of one or more ADs was indicative of poor outcomes in speech production and educational placement. As shown in Table 1, the outcome predictors identified in these two studies were rather different, highlighting a wide range of demographic, environmental, cultural, socioeconomic, and medical factors contributing to speech perception outcomes.

MRI and Electrophysiological Predictors of CI Outcomes

Preoperative MRI Evidence: The ANSD clinical diagnosis is based on (a) objective electrophysiological measures of cochlear hair cells and auditory nerve function, (b) imaging of auditory nerve/brainstem, and (c) behavioral audiological assessments. Approximately one-third of children with ANSD are identified with CND (i.e., aplasia and hypoplasia). CND was initially described in 1997 (Casselman et al., 1997). Aplasia and hypoplasia are defined based on MRI findings. Patients with CND often present with associated labyrinthine abnormalities, with widely

varying degrees of severity (Peng et al., 2017). Moreover, they are at higher risk of intracranial abnormalities and deficits in the central nervous system (CNS) (Hall, 2015). Based on the MRI results:

- The cochlear nerve is considered normal if it is the same size or larger than the facial nerve (Casselman et al., 1997).
- The nerve is deficient if it is smaller than the facial nerve (i.e., hypoplasia). In this case, the nerve is described as small or rudimentary.
- The nerve is considered absent if not seen on axial, coronal, or sagittal images (i.e., aplasia) (Glastonbury et al., 2002). In addition, a small nerve beyond scanner resolution may be considered absent.

Likewise, the cochlear nerve canal (CNC) is characterized as normal if the vertical or transverse diameter is four millimeters or more (Glastonbury et al., 2002), narrow if the diameter is two to three millimeters (Jackler et al., 1987), and stenotic if less than two millimeters (Valvassori and Pierce, 1964). Measurements are taken from the narrowest portion of CNC. Overall, CIs are always conducted on children with CND before offering auditory brainstem implants (ABI) (Wolfe, 2020).

In a study in Australia, Walton et al. (2008) used MRI findings to divide children with ANSD into two groups, including 15 children with CND and 39 children without CND. The two groups were compared in speech perception scores one-year post-implantation. Intraoperative eABR was abnormal in 13 out of 15 (87%) children with CND relative to 9 out of 39 (23%) children without CND. Children in both groups with abnormal eABR had significantly lower speech perception scores, and eABR results were significantly reduced in children with CND compared to those without CND. The findings of this study suggested a higher rate of abnormal

eABR and poor speech perception outcomes in children with CND relative to children without CND (Walton et al., 2008).

Table 1. Studies on predictors of amplification outcomes

Study	Country	Study design	Sample size	Age at HL diagnosis (months)	Age at HAs (months)	Age at CIs (months)	Predictors
Ching et al. 2013b	Australia	Pros	451 in total, 47 children with ANSD	6.00 (8.20)	8.90 (8.80)	17.70 (9.00)	Presence of ADs, female sex, higher maternal education, age at CI
le Roux et al. 2016	South Africa	Retro	301	16.10 (10.00)	NR	45.60 (32.50)	Use of two CIs, oral mode of communication, mainstream education, NICU admission, prematurity, ADs, ethnicities other than Caucasians

ADs: additional disabilities, ANSD: auditory neuropathy spectrum disorder, CI: cochlear implant, HA: hearing aid, HL: hearing loss, NICU: neonatal intensive care unit, Pros: prospective, Retro: retrospective.

Electric Compound Action Potential (eCAP): eCAP, which is similar to the first wave of ABR, is an electrophysiological test that measures the auditory nerve response to electrical stimulation after the insertion of CI electrodes. Neural response telemetry (NRT), neural response imaging (NRI), or auditory nerve response telemetry (ART) is a technique used to measure eCAP intraoperatively. eCAP results within normal limits are suggestive of the potential success of the cochlear implant

and help verify the proper placement and function of electrodes (Cosetti et al., 2010; Sawaf et al., 2022).

In the Peterson et al. (2003) study, NRT was recorded in all children with ANSD and peers with SNHL, and the two groups showed no significant difference in NRT findings and speech performance scores. In another study on 16 children with ANSD and their peers with SNHL, the two groups performed equally in speech recognition tests in both quiet and noise conditions (Attias et al., 2017). However, the ANSD group showed a significant decline in NRT results (i.e., significantly lower electrical thresholds for each electrode, lower comfortable levels, lower mean electrical dynamic range, and lower mean predicted NRT thresholds [tNRT] for basal and apical electrodes) compared to the control group. tNRT is usually estimated using either linear extrapolation of the amplitude growth function, or visual detection of the smallest measurable neural response (Lai et al., 2009). In the Cosetti et al. (2010) study on a large group of children and adults with SNHL (n = 97), no relationship was found between tNRT responses and open-set speech performance at 1-year post-CI.

Pre/postoperative eABR: eABR is characterized by three positive peaks (eII, eIII, and eV) generated from the auditory nerve, cochlear nucleus, and possibly neurons in the lateral lemniscus or inferior colliculus. Wave I is usually hidden by stimulus artifacts and preamplifier distortion. eABR has a larger amplitude and shorter latency compared to acoustic ABR and shows a steeper latency-intensity function (Firszt et al., 2002; Gordon et al., 2006). Preoperative eABR is an electrophysiological diagnostic assessment that assists in (1) determining whether the cochlear nerve is electrically excitable, (2) identifying which ear is the most appropriate ear for implantation, (3) characterizing the site of pathology in ANSD, and 4) providing clinicians with information about the prognosis of CIs (Gibson and Sanli, 2000; Kim et al., 2008). However,

inconsistencies are observed in the literature on the prognostic value of intraoperative eABR in post-CI outcomes. For example, in Gibson et al. (2009) study on children with severe to profound SNHL as well as in Dutt et al. (2021) study on children with ANSD, better speech perception scores were associated with higher eABR waveform scores (Dutt et al., 2021; Gibson et al., 2009) (eABR waveform scoring method: 3 = present eII, eIII, eIV-V; 2 = absent eII, present eIII, and eIV-V; 1 = only present eIV-V; 0 = absent all waves). In two other studies on children with ANSD (Jeong and Kim, 2013) and SNHL (Nikolopoulos et al., 2000), eABR, however, was not a reliable predictor of post-CI speech perception abilities. In Walton et al. (2008) study, lower speech perception scores were found in children with abnormal eABR irrespective of the existence of CND (Walton et al., 2008). In Jeon et al. (2013) study, eABR was not detected in more than half of children with ANSD. In addition, children with ANSD and present eABR showed variability in wave V latency and amplitude as well as CI outcomes.

In a retrospective study by Yamazaki et al. (2015) on 19 children with CND, both MRI and eABR measures were individually associated with CI outcomes. The authors concluded that the combination of MRI and eABR results was a proper approach to classifying poor, moderate, and good CI outcomes. For example, all children with cranial never VII (CN7) greater than CN8 and no eV achieved postoperative CAP scores ≤ 3, while children with CN7 equal or smaller than CN8 and present eV had CAP scores ≥ 3.

Amplification Outcomes in Children with ANSD

According to the American Academy of Audiology (AAA) pediatric amplification guidelines, children with ANSD may or may not progress in speech understanding with amplification (AAA, 2013). It is well-accepted that the lack of auditory stimulation during the

critical period of spoken language development results in delays in auditory, speech, language, social, emotional, and cognitive development (Dillon et al., 2013; Robertson et al., 2009; Yoshinaga-Itano et al., 1998). Since the beginning of EHDI programs, findings of several studies indicate the benefits of EHDI for speech perception outcomes in ANSD (Ambrose et al., 2014; Cowan et al., 2018; Cupples et al., 2018; Tomblin et al., 2015; Wolfe, 2020).

Management of ANSD is challenging and requires the involvement of a team of medical and non-medical professionals from audiology, speech-language pathology, medicine (e.g., otolaryngology, pediatrics, neurology), genetics, and sometimes occupational and physical therapy (due to additional disabilities) (Hall, 2015). Depending on the lesion site and auditory and speech perception performance, management options could be different from no amplification at all to frequency modulating (FM) systems, HAs, and CIs (Humphriss et al., 2013). Conventional HAs may be used to amplify the acoustic signal and improve speech audibility in ANSD. According to AAA Pediatric Amplification Guidelines, a HA trial is recommended for children with permanent HL when behavioral hearing thresholds interfere with speech perception at conversational levels (Walker et al., 2016). Although HAs may be beneficial for speech recognition in mild to moderate hearing loss 2001), they may not be effective due to poor processing of auditory temporal cues in ANSD (Berlin et al., 2010; Ching et al., 2013c; De Siati et al., 2020; Kaga, 2016; Rance, 2005; Rance et al., 2002; Starr et al., 1996). Indeed, conventional HAs amplify the signal but are unable to overcome impaired speech comprehension due to neural dyssynchrony. For example, in a large multicentric study, Berlin et al. (2010) reported the outcomes of HAs (n = 85) and CIs (n = 49) in children and adults with ANSD. While HAs were described as offering good benefit, some benefit,

little benefit, and no benefit by 3.53%, 10.59%, 24.71%, and 61.17% of individuals, respectively, successful speech recognition outcomes were reported in 85% of CI recipients.

CIs consist of a surgically implanted device and an externally worn speech processor. The internal processor takes advantage of the tonotopic organization of the basilar membrane and transfers processed information to electrodes located at different positions within the cochlea. Stimulation of these electrodes provides localized excitation of cochlear nerve fibers leading to the discrimination of the corresponding pitch information required to comprehend speech (Katz et al., 2015). Cochlear implantation is one of the most successful neuroprosthetic devices in rehabilitation (Kuchta, 2007; Lim et al., 2009). This success rate results from the fact that the perception of auditory information is largely based on temporal processing, which can be properly transmitted by only a few electrodes (Kuchta, 2007). In addition, the auditory nerve is better stimulated and synchronized with electric stimulation relative to acoustic stimulation (Chaudhry et al., 2020). A CI bypasses the cochlear and synaptic parts of the auditory system and directly stimulates spiral ganglion neurons. This direct electrical transmission of auditory signals to the brain provides greater support for the development of fundamental hearing and speech perception skills (Chaudhry et al., 2020; Shearer and Hansen, 2019). CIs are a feasible option when children show poor progress with properly fitted HAs (JCIH, 2019). While most children with SNHL can achieve typical rates of speech, language, and academic development (Leigh et al., 2011), the CI outcomes of children with ANSD vary widely (Bo et al., 2022; Cupples et al., 2018; Myers and Nicholson, 2021; Peng et al., 2017; Rajput et al., 2019; Rance and Starr, 2015; Vesseur et al., 2018), and demonstrate a direct association with the lesion site(s). Thus, close examination of

auditory behavioral, electrophysiological, and MRI findings is essential to decide on proper auditory interventions (Rance and Starr, 2015).

Presynaptic ANSD and CI: Individuals with a presynaptic form of auditory neuropathy, due to the loss of IHC and/or dysfunction or abnormality of IHC ribbon synapses, predominately achieve good CI outcomes similar to their peers with SNHL (Fayad and Linthicum, 2006; Rance and Starr, 2015; Rodríguez-Ballesteros et al., 2003; Santarelli et al., 2015). In these patients, electrically evoked auditory potentials (i.e., eCAP and eABR) reflect an increase in the number of fibers activated and/or their synchrony of discharge (Rance and Starr, 2015).

Postsynaptic ANSD and CI: Due to the diversity of the lesion site in postsynaptic ANSD (i.e., auditory nerve dendrites, dendrites and axons, ganglion cells, myelin, auditory nerve, and/or brainstem), different pathological mechanisms (i.e., diminished auditory nerve fibers, dyssynchronous nerve activity, hypoplasia/aplasia, and/or conduction disorders) and variable degrees of neural disruption are expected. Some patients may have speech perception equivalent to their peers with SNHL, while others may achieve no auditory perception of electrical stimulation or functionally useful hearing. Other patients may progress between these two (Bo et al., 2022; Chaudhry et al., 2020; Humphriss et al., 2013; Peng et al., 2017; Rance and Starr, 2015; Vesseur et al., 2018).

A Short Overview of the Following Chapters

This doctoral thesis entails three consecutive associated projects on children with ANSD, consistent with the three primary objectives of the thesis. Chapter 2 (i.e., the first project) presents the results of a retrospective chart review to determine factors with predictive value to post-

intervention (CIs and/or HAs) outcomes. In this project, the records of 38 children with ANSD, who used CIs and/or HAs, identified at the Children's Hospital of Eastern Ontario (CHEO) were reviewed. Chapter three (i.e., the second project) is an SR of existing evidence over the prognostic value of early auditory electrophysiologic tests and MRI findings for CI outcomes, and chapter 4 (i.e., the third project) is an overview of existing SR on CI outcomes in children with ANSD. For the second and third projects, the SRs were guided by the PRISMA 2020 statement, and electronic databases were searched without restrictions on language, publication status, or year of publication. In the second project, studies on children with ANSD, cochleovestibular nerve (CVN) abnormalities, or SNHL reporting the relevance of preoperative and/or postoperative eCAP, eABR, and/or MRI results to CI outcomes were included. The methodological quality and strength of evidence were assessed using the Crowe Critical Appraisal Tool (CCAT) and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool, respectively. In the third project, the methodological quality of the selected SRs was evaluated using the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) checklist, and the risk of bias in evidence was assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool. The last chapter of the current thesis (i.e., chapter five) summarizes the findings of the three projects and limitations in existing evidence and provides grand conclusions and directions for future research.

References

AAA, 2013. American Academy of Audiology. Clinical practice guidelines: Pediatric amplification.

Ambrose, S.E., Unflat Berry, L.M., Walker, E.A., Harrison, M., Oleson, J., Moeller, M.P. (2014). Speech sound production in 2-year-olds who are hard of hearing. *Am J Speech Lang Pathol*. 23(2), 91-104. doi:10.1044/2014_ajslp-13-0039.

Attias, J., Greenstein, T., Peled, M., Ulanovski, D., Wohlgelernter, J., Raveh, E. (2017). Auditory Performance and Electrical Stimulation Measures in Cochlear Implant Recipients With Auditory Neuropathy Compared With Severe to Profound Sensorineural Hearing Loss. *Ear Hear*. 38(2), 184-193. doi:10.1097/aud.0000000000000384.

Berlin, C.I., Hood, L., Morlet, T., Rose, K., Brashears, S. (2003). Auditory neuropathy/dys-synchrony: diagnosis and management. *Ment Retard Dev Disabil Res Rev*. 9(4), 225-231. doi:10.1002/mrdd.10084.

Berlin, C.I., Hood, L.J., Morlet, T., Wilensky, D., Li, L., Mattingly, K.R., Taylor-Jeanfreau, J., Keats, B.J., John, P.S., Montgomery, E., Shallop, J.K., Russell, B.A., Frisch, S.A. (2010). Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-synchrony (auditory neuropathy spectrum disorder). *Int J Audiol*. 49(1), 30-43. doi:10.3109/14992020903160892.

Bielecki, I., Horbulewicz, A., Wolan, T. (2012). Prevalence and risk factors for auditory neuropathy spectrum disorder in a screened newborn population at risk for hearing loss. *Int J Pediatr Otorhinolaryngol*. 76(11), 1668-1670. doi:10.1016/j.ijporl.2012.08.001

Bo, D., Huang, Y., Wang, B., Lu, P., Chen, W.X., Xu, Z.M. (2022). Auditory and Speech Outcomes of Cochlear Implantation in Children With Auditory Neuropathy Spectrum Disorder: A Systematic Review and Meta-Analysis. *Ann Otol Rhinol Laryngol*, 34894221092201. doi:10.1177/00034894221092201.

Casselman, J.W., Offeciers, F.E., Govaerts, P.J., Kuhweide, R., Geldof, H., Somers, T., D'Hont, G. (1997). Aplasia and hypoplasia of the vestibulocochlear nerve: diagnosis with MR imaging. *Radiology*. 202(3), 773-781. doi:10.1148/radiology.202.3.9051033.

Ceranić, B., Luxon, L.M. (2004). Progressive auditory neuropathy in patients with Leber's hereditary optic neuropathy. *J Neurol Neurosurg Psychiatry*. 75(4), 626-630. doi:10.1136/jnnp.2003.017673.

Chao, X., Luo, J., Fan, Z., Shi, H., Han, Y., Wang, R., Song, Y., Wang, G., Wang, H., Xu, L. (2016). Usefulness of radiological findings for predicting cochlear implantation outcomes in children with cochlear nerve deficiency: a pilot study. *Acta Otolaryngol*. 136(10), 1051-1057. doi:10.1080/00016489.2016.1179788.

Chaudhry, D., Chaudhry, A., Muzaffar, J., Monksfield, P., Bance, M. (2020). Cochlear Implantation Outcomes in Post Synaptic Auditory Neuropathies: A Systematic Review and Narrative Synthesis. *J Int Adv Otol*. 16(3), 411-431. doi:10.5152/iao.2020.9035.

Ching, T.Y., Day, J., Dillon, H., Gardner-Berry, K., Hou, S., Seeto, M., Wong, A., Zhang, V. (2013a). Impact of the presence of auditory neuropathy spectrum disorder (ANSD) on outcomes of children at three years of age. *Int J Audiol*. 52 Suppl 2(0 2), S55-64. doi:10.3109/14992027.2013.796532.

Ching, T.Y., Dillon, H., Marnane, V., Hou, S., Day, J., Seeto, M., Crowe, K., Street, L., Thomson, J., Van Buynder, P., Zhang, V., Wong, A., Burns, L., Flynn, C., Cupples, L., Cowan, R.S., Leigh, G., Sjahalam-King, J., Yeh, A. (2013b). Outcomes of early- and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear Hear*. 34(5), 535-552. doi:10.1097/AUD.0b013e3182857718.

Ching, T.Y.C., Day, J., Dillon, H., Gardner-Berry, K., Hou, S., Seeto, M., Wong, A., Zhang, V. (2013c). Impact of the presence of auditory neuropathy spectrum disorder (ANSD) on outcomes of children at three years of age. *Int J Audiol*. 52 Suppl 2(0 2), S55-64. doi:10.3109/14992027.2013.796532.

Ching, T.Y.C., Dillon, H., Leigh, G., Cupples, L. (2018). Learning from the Longitudinal Outcomes of Children with Hearing Impairment (LOCHI) study: summary of 5-year findings and implications. *Int J Audiol*. 57(sup2), S105-s111. doi:10.1080/14992027.2017.1385865.

Cosetti, M.K., Shapiro, W.H., Green, J.E., Roman, B.R., Lalwani, A.K., Gunn, S.H., Roland, J.T., Jr., Waltzman, S.B. (2010). Intraoperative neural response telemetry as a predictor of performance. *Otol Neurotol*. 31(7), 1095-1099. doi:10.1097/MAO.0b013e3181ec1b8c

Cowan, R.S.C., Edwards, B., Ching, T.Y.C. (2018). Longitudinal outcomes of children with hearing impairment (LOCHI): 5-year data. *Int J Audiol*. 57(sup2), S1-s2. doi:10.1080/14992027.2018.1458703.

Cupples, L., Ching, T.Y.C., Button, L., Leigh, G., Marnane, V., Whitfield, J., Gunnourie, M., Martin, L. (2018). Language and speech outcomes of children with hearing loss and additional disabilities: identifying the variables that influence performance at five years of age. *Int J Audiol*. 57(sup2), S93-s104. doi:10.1080/14992027.2016.1228127.

De Siati, R.D., Rosenzweig, F., Gersdorff, G., Gregoire, A., Rombaux, P., Deggouj, N. (2020). Auditory Neuropathy Spectrum Disorders: From Diagnosis to Treatment: Literature Review and Case Reports. *J Clin Med*. 9(4). doi:10.3390/jcm9041074.

Dechartres, A., Trinquart, L., Boutron, I., Ravaud, P. (2013). Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *Bmj*. 346, f2304. doi:10.1136/bmj.f2304.

Dillon, H., Cowan, R., Ching, T.Y. (2013). Longitudinal outcomes of children with hearing impairment (LOCHI). *Int J Audiol*. 52 Suppl 2, S2-3. doi:10.3109/14992027.2013.866448

Dutt, S.N., Kumar, A., Mittal, A.A., Vadlamani, S., Gaur, S.K. (2021). Cochlear implantation in auditory neuropathy spectrum disorders: role of transtympanic electrically evoked auditory brainstem responses and serial neural response telemetry. *J Laryngol Otol*. 135(7), 602-609. doi:10.1017/s0022215121001328.

Fayad, J.N., Linthicum, F.H., Jr. (2006). Multichannel cochlear implants: relation of histopathology to performance. *Laryngoscope*. 116(8), 1310-1320. doi:10.1097/01.mlg.0000227176.09500.28.

Fernandes, N.F., Morettin, M., Yamaguti, E.H., Costa, O.A., Bevilacqua, M.C. (2015). Performance of hearing skills in children with auditory neuropathy spectrum disorder using cochlear implant: a systematic review. *Braz J Otorhinolaryngol*. 81(1), 85-96. doi:10.1016/j.bjorl.2014.10.003.

Firszt, J.B., Chambers, R.D., Kraus, Reeder, R.M. (2002). Neurophysiology of cochlear implant users I: effects of stimulus current level and electrode site on the electrical ABR, MLR, and N1-P2 response. *Ear Hear*. 23(6), 502-515. doi:10.1097/00003446-200212000-00002

Gardner-Berry, K., Hou, S., Ching, T., 2019. Managing infants and children with auditory neuropathy spectrum disorder. In: Madell, J., Flexer, C., Wolfe, J., Schafer, E. (Eds.), Pediatric audiology: Diagnosis, technology, and management, 3rd ed. ed. Thieme Medical, New York.

Gibson, W., Sanli, H., 2000. The role of round window electrophysiological techniques in the selection of children for cochlear implants. In: Kim, C., Chang, S., Lim, D. (Eds.), Advances in Oto-Rhino-Laryngology. Karger, Basel, pp. 148-151.

Gibson, W.P., Sanli, H. (2007). Auditory neuropathy: an update. *Ear Hear*. 28(2 Suppl), 102s-106s. doi:10.1097/AUD.0b013e3180315392.

Gibson, W.P., Sanli, H., Psarros, C. (2009). The use of intra-operative electrical auditory brainstem responses to predict the speech perception outcome after cochlear implantation. *Cochlear Implants Int*. 10 Suppl 1, 53-57. doi:10.1179/cim.2009.10.Supplement-1.53.

Glastonbury, C.M., Davidson, H.C., Harnsberger, H.R., Butler, J., Kertesz, T.R., Shelton, C. (2002). Imaging findings of cochlear nerve deficiency. *AJNR Am J Neuroradiol*. 23(4), 635-643.

Gordon, K.A., Papsin, B.C., Harrison, R.V. (2006). An evoked potential study of the developmental time course of the auditory nerve and brainstem in children using cochlear implants. *Audiol Neurootol*. 11(1), 7-23. doi:10.1159/000088851.

Hall, J., 2015. eHandbook of Auditory Evoked Responses: Principles, Procedures & Protocols. Pearson Education, Inc.

Hayes, D., Sininger, Y., 2008. Guidelines for Identification and Management of Infants and Young Children with Auditory Neuropathy Spectrum Disorder, NHS 2008, Como, Italy.

He, S., Grose, J., Teagle, H., Woodard, J., Park, L., Hatch, D., Roush, P., Buchman, C. (2015). Acoustically evoked auditory change complex in children with auditory neuropathy spectrum disorder: a potential objective tool for identifying cochlear implant candidates. *Ear Hear*. 36(3), 289-301. doi:10.1097/aud.0000000000000119.

Holcomb, M.A., Rumboldt, Z., White, D.R. (2013). Cochlear nerve deficiency in children with CHARGE syndrome. *Laryngoscope*. 123(3), 793-796. doi:10.1002/lary.23682.

Huang, B.Y., Zdanski, C., Castillo, M. (2012). Pediatric sensorineural hearing loss, part 2: syndromic and acquired causes. *AJNR Am J Neuroradiol*. 33(3), 399-406. doi:10.3174/ajnr.A2499.

Humphriss, R., Hall, A., Maddocks, J., Macleod, J., Sawaya, K., Midgley, E. (2013). Does cochlear implantation improve speech recognition in children with auditory neuropathy spectrum disorder? A systematic review. *Int J Audiol*. 52(7), 442-454. doi:10.3109/14992027.2013.786190.

Jackler, R.K., Luxford, W.M., House, W.F. (1987). Congenital malformations of the inner ear: a classification based on embryogenesis. *Laryngoscope*. 97(3 Pt 2 Suppl 40), 2-14. doi:10.1002/lary.5540971301.

Jeon, J.H., Bae, M.R., Song, M.H., Noh, S.H., Choi, K.H., Choi, J.Y. (2013). Relationship between electrically evoked auditory brainstem response and auditory performance after cochlear implant in patients with auditory neuropathy spectrum disorder. *Otol Neurotol*. 34(7), 1261-1266. doi:10.1097/MAO.0b013e318291c632.

Jeong, S.W., Kim, L.S. (2013). Auditory neuropathy spectrum disorder: predictive value of radiologic studies and electrophysiologic tests on cochlear implant outcomes and its radiologic classification. *Acta Otolaryngol*. 133(7), 714-721. doi:10.3109/00016489.2013.776176.

Kaga, K. (2016). Auditory nerve disease and auditory neuropathy spectrum disorders. *Auris Nasus Larynx*. 43(1), 10-20. doi:10.1016/j.anl.2015.06.008.

Kari, E., Gillard, D.M., Chuang, N., Go, J.L. (2022). Can Imaging Predict Hearing Outcomes in Children With Cochleovestibular Nerve Abnormalities? *Laryngoscope*. 132 Suppl 8, S1-s15. doi:10.1002/lary.30008.

Katz, J., Chasin, M., English, K., Hood, L.J., Tillery, K.L., 2015. Handbook of Clinical Audiology, Seventh Edition ed. Wolters Kluwer Health, Philadelphia.

Kim, A.H., Kileny, P.R., Arts, H.A., El-Kashlan, H.K., Telian, S.A., Zwolan, T.A. (2008). Role of electrically evoked auditory brainstem response in cochlear implantation of children with inner ear malformations. *Otol Neurotol*. 29(5), 626-634. doi:10.1097/MAO.0b013e31817781f5.

Korver, A.M., van Zanten, G.A., Meuwese-Jongejeugd, A., van Straaten, H.L., Oudesluys-Murphy, A.M. (2012). Auditory neuropathy in a low-risk population: a review of the literature. *Int J Pediatr Otorhinolaryngol*. 76(12), 1708-1711. doi:10.1016/j.ijporl.2012.08.009.

Kuchta, J. (2007). Twenty-five years of auditory brainstem implants: perspectives. *Acta Neurochir Suppl*. 97(Pt 2), 443-449. doi:10.1007/978-3-211-33081-4_51.

Lai, W.K., Dillier, N., Weber, B.P., Lenarz, T., Battmer, R., Gantz, B., Brown, C., Cohen, N., Waltzman, S., Skinner, M., Holden, L., Cowan, R., Busby, P., Killian, M. (2009). TNRT profiles with the nucleus research platform 8 system. *Int J Audiol*. 48(9), 645-654. doi:10.1080/14992020902962413.

le Roux, T., Vinck, B., Butler, I., Cass, N., Louw, L., Nauta, L., Schlesinger, D., Soer, M., Tshifularo, M., Swanepoel de, W. (2016). Predictors of pediatric cochlear implantation outcomes in South Africa. *Int J Pediatr Otorhinolaryngol*. 84, 61-70. doi:10.1016/j.ijporl.2016.02.025.

Leigh, J., Dettman, S., Dowell, R., Sarant, J. (2011). Evidence-based approach for making cochlear implant recommendations for infants with residual hearing. *Ear Hear*. 32(3), 313-322. doi:10.1097/AUD.0b013e3182008b1c

Lim, H.H., Lenarz, M., Lenarz, T. (2009). Auditory midbrain implant: a review. *Trends Amplif*. 13(3), 149-180. doi:10.1177/1084713809348372.

Madden, C., Rutter, M., Hilbert, L., Greinwald, J.H., Jr., Choo, D.I. (2002). Clinical and audiological features in auditory neuropathy. *Arch Otolaryngol Head Neck Surg*. 128(9), 1026-1030. doi:10.1001/archotol.128.9.1026.

Maeda-Katahira, A., Nakamura, N., Hayashi, T., Katagiri, S., Shimizu, S., Ohde, H., Matsunaga, T., Kaga, K., Nakano, T., Kameya, S., Matsuura, T., Fujinami, K., Iwata, T., Tsunoda, K. (2019). Autosomal dominant optic atrophy with OPA1 gene mutations accompanied by auditory neuropathy and other systemic complications in a Japanese cohort. *Mol Vis*. 25, 559-573.

Manchaiah, V.K., Zhao, F., Danesh, A.A., Duprey, R. (2011). The genetic basis of auditory neuropathy spectrum disorder (ANSD). *Int J Pediatr Otorhinolaryngol*. 75(2), 151-158. doi:10.1016/j.ijporl.2010.11.023.

Mittal, R., Ramesh, A.V., Panwar, S.S., Nilkanthan, A., Nair, S., Mehra, P.R. (2012). Auditory neuropathy spectrum disorder: its prevalence and audiological characteristics in an Indian tertiary care hospital. *Int J Pediatr Otorhinolaryngol*. 76(9), 1351-1354. doi:10.1016/j.ijporl.2012.06.005.

Moser, T., Starr, A. (2016). Auditory neuropathy--neural and synaptic mechanisms. *Nat Rev Neurol*. 12(3), 135-149. doi:10.1038/nrneurol.2016.10.

Myers, K., Nicholson, N. (2021). Cochlear Implant Behavioral Outcomes for Children With Auditory Neuropathy Spectrum Disorder: A Mini-Systematic Review. *Am J Audiol*. 30(3), 777-789. doi:10.1044/2021_aja-20-00175.

Nada, N., Kolkaila, E., Schendzielorz, P., El Mahallawi, T. (2022). Electrically evoked auditory brainstem response in cochlear implantation: what you need to know (short review). *The Egyptian Journal of Otolaryngology*. 38(67), 1-8. doi:doi.org/10.1186/s43163-022-00259-1.

Nikolopoulos, T.P., Mason, S.M., Gibbin, K.P., O'Donoghue, G.M. (2000). The prognostic value of promontory electric auditory brain stem response in pediatric cochlear implantation. *Ear Hear*. 21(3), 236-241. doi:10.1097/00003446-200006000-00007.

Niparko, J.K., Tobey, E.A., Thal, D.J., Eisenberg, L.S., Wang, N.Y., Quittner, A.L., Fink, N.E. (2010). Spoken language development in children following cochlear implantation. *Jama*. 303(15), 1498-1506. doi:10.1001/jama.2010.451.

Peng, K.A., Kuan, E.C., Hagan, S., Wilkinson, E.P., Miller, M.E. (2017). Cochlear Nerve Aplasia and Hypoplasia: Predictors of Cochlear Implant Success. *Otolaryngol Head Neck Surg*. 157(3), 392-400. doi:10.1177/0194599817718798.

Petersen, M.B., Willems, P.J. (2006). Non-syndromic, autosomal-recessive deafness. *Clin Genet*. 69(5), 371-392. doi:10.1111/j.1399-0004.2006.00613.x

Peterson, A., Shallop, J., Driscoll, C., Breneman, A., Babb, J., Stoeckel, R., Fabry, L. (2003). Outcomes of cochlear implantation in children with auditory neuropathy. *J Am Acad Audiol*. 14(4), 188-201.

Rajput, K., Saeed, M., Ahmed, J., Chung, M., Munro, C., Patel, S., Leal, C., Jiang, D., Nash, R. (2019). Findings from aetiological investigation of Auditory Neuropathy Spectrum

Disorder in children referred to cochlear implant programs. *Int J Pediatr Otorhinolaryngol*. 116, 79-83. doi:10.1016/j.ijporl.2018.10.010.

Rance, G. (2005). Auditory neuropathy/dys-synchrony and its perceptual consequences. *Trends Amplif*. 9(1), 1-43. doi:10.1177/108471380500900102.

Rance, G., Cone-Wesson, B., Wunderlich, J., Dowell, R. (2002). Speech perception and cortical event-related potentials in children with auditory neuropathy. *Ear Hear*. 23(3), 239-253. doi:10.1097/00003446-200206000-00008.

Rance, G., Corben, L., Delatycki, M. (2012a). Auditory processing deficits in children with Friedreich ataxia. *J Child Neurol*. 27(9), 1197-1203. doi:10.1177/0883073812448963.

Rance, G., McKay, C., Grayden, D. (2004). Perceptual characterization of children with auditory neuropathy. *Ear Hear*. 25(1), 34-46. doi:10.1097/01.aud.0000111259.59690.b8.

Rance, G., Ryan, M.M., Bayliss, K., Gill, K., O'Sullivan, C., Whitechurch, M. (2012b). Auditory function in children with Charcot-Marie-Tooth disease. *Brain*. 135(Pt 5), 1412-1422. doi:10.1093/brain/aws085.

Rance, G., Starr, A., 2011. Auditory neuropathy/dys-synchrony. In: Seewald, R., Tharpe, A. (Eds.), Comprehensive handbook of pediatric audiology Plural Publishing, San Diego, pp. 225-242.

Rance, G., Starr, A. (2015). Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. *Brain*. 138(Pt 11), 3141-3158. doi:10.1093/brain/awv270.

Rea, P.A., Gibson, W.P. (2003). Evidence for surviving outer hair cell function in congenitally deaf ears. *Laryngoscope*. 113(11), 2030-2034. doi:10.1097/00005537-200311000-00033.

Robertson, C.M., Howarth, T.M., Bork, D.L., Dinu, I.A. (2009). Permanent bilateral sensory and neural hearing loss of children after neonatal intensive care because of extreme

prematurity: a thirty-year study. *Pediatrics*. 123(5), e797-807. doi:10.1542/peds.2008-2531.

Roche, J.P., Huang, B.Y., Castillo, M., Bassim, M.K., Adunka, O.F., Buchman, C.A. (2010). Imaging characteristics of children with auditory neuropathy spectrum disorder. *Otol Neurotol*. 31(5), 780-788. doi:10.1097/mao.0b013e3181d8d528.

Rodríguez-Ballesteros, M., del Castillo, F.J., Martín, Y., Moreno-Pelayo, M.A., Morera, C., Prieto, F., Marco, J., Morant, A., Gallo-Terán, J., Morales-Angulo, C., Navas, C., Trinidad, G., Tapia, M.C., Moreno, F., del Castillo, I. (2003). Auditory neuropathy in patients carrying mutations in the otoferlin gene (OTOF). *Hum Mutat*. 22(6), 451-456. doi:10.1002/humu.10274.

Roush, P., Frymark, T., Venediktov, R., Wang, B. (2011). Audiologic management of auditory neuropathy spectrum disorder in children: a systematic review of the literature. *Am J Audiol*. 20(2), 159-170. doi:10.1044/1059-0889(2011/10-0032).

Ruel, J., Emery, S., Nouvian, R., Bersot, T., Amilhon, B., Van Rybroek, J.M., Rebillard, G., Lenoir, M., Eybalin, M., Delprat, B., Sivakumaran, T.A., Giros, B., El Mestikawy, S., Moser, T., Smith, R.J., Lesperance, M.M., Puel, J.L. (2008). Impairment of SLC17A8 encoding vesicular glutamate transporter-3, VGLUT3, underlies nonsyndromic deafness DFNA25 and inner hair cell dysfunction in null mice. *Am J Hum Genet*. 83(2), 278-292. doi:10.1016/j.ajhg.2008.07.008.

Saidia, A.R., Ruel, J., Bahloul, A., Chaix, B., Venail, F., Wang, J. (2023). Current Advances in Gene Therapies of Genetic Auditory Neuropathy Spectrum Disorder. *J Clin Med*. 12(3). doi:10.3390/jcm12030738.

Santarelli, R., del Castillo, I., Cama, E., Scimemi, P., Starr, A. (2015). Audibility, speech perception and processing of temporal cues in ribbon synaptic disorders due to OTOF mutations. *Hear Res*. 330(Pt B), 200-212. doi:10.1016/j.heares.2015.07.007.

Santarelli, R., Scimemi, P., La Morgia, C., Cama, E., Del Castillo, I., Carelli, V. (2021). Electrocochleography in Auditory Neuropathy Related to Mutations in the OTOF or OPA1 Gene. *Audiol Res*. 11(4), 639-652. doi:10.3390/audiolres11040059.

Sawaf, T., Vovos, R., Hadford, S., Woodson, E., Anne, S. (2022). Utility of intraoperative neural response telemetry in pediatric cochlear implants. *Int J Pediatr Otorhinolaryngol*. 162, 111298. doi:10.1016/j.ijporl.2022.111298.

Shearer, A.E., Hansen, M.R. (2019). Auditory synaptopathy, auditory neuropathy, and cochlear implantation. *Laryngoscope Investig Otolaryngol*. 4(4), 429-440. doi:10.1002/lio2.288

Sininger, Y., Oba, S., 2001. Patients with auditory neuropathy: Who are they and what can they hear? In: Sininger, Y., Starr, A. (Eds.), Auditory Neuropathy. Singular Publishing, San Diego, pp. 15-36.

Starr, A., McPherson, D., Patterson, J., Don, M., Luxford, W., Shannon, R., Sininger, Y., Tonakawa, L., Waring, M. (1991). Absence of both auditory evoked potentials and auditory percepts dependent on timing cues. *Brain*. 114 (Pt 3), 1157-1180. doi:10.1093/brain/114.3.1157.

Starr, A., Picton, T.W., Sininger, Y., Hood, L.J., Berlin, C.I. (1996). Auditory neuropathy. *Brain*. 119 (Pt 3), 741-753. doi:10.1093/brain/119.3.741

Starr, A., Rance, G., 2015. Auditory neuropathy. in: Celesia, G., Hickok, G. (Eds.), Handbook of Clinical Neurology. Elsevier, Edinburgh pp. 495-508.

Surel, C., Guillet, M., Lenoir, M., Bourien, J., Sendin, G., Joly, W., Delprat, B., Lesperance, M.M., Puel, J.L., Nouvian, R. (2016). Remodeling of the Inner Hair Cell Microtubule Meshwork in a Mouse Model of Auditory Neuropathy AUNA1. *eNeuro*. 3(6). doi:10.1523/eneuro.0295-16.2016.

Teagle, H.F., Roush, P.A., Woodard, J.S., Hatch, D.R., Zdanski, C.J., Buss, E., Buchman, C.A. (2010). Cochlear implantation in children with auditory neuropathy spectrum disorder. *Ear Hear*. 31(3), 325-335. doi:10.1097/AUD.0b013e3181ce693b.

Tomblin, J.B., Harrison, M., Ambrose, S.E., Walker, E.A., Oleson, J.J., Moeller, M.P. (2015). Language Outcomes in Young Children with Mild to Severe Hearing Loss. *Ear Hear*. 36 Suppl 1(0 1), 76s-91s. doi:10.1097/aud.0000000000000219.

Trecca, E.M.C., Riggs, W.J., Mattingly, J.K., Hiss, M.M., Cassano, M., Adunka, O.F. (2020). Electrocochleography and Cochlear Implantation: A Systematic Review. *Otol Neurotol*. 41(7), 864-878. doi:10.1097/mao.0000000000002694.

Valvassori, G.E., Pierce, R.H. (1964). The Normal InternL Auditory Canal. *Am J Roentgenol Radium Ther Nucl Med*. 92, 1232-1241.

Vesseur, A., Free, R., Snels, C., Dekker, F., Mylanus, E., Verbist, B., Frijns, J. (2018). Hearing Restoration in Cochlear Nerve Deficiency: the Choice Between Cochlear Implant or Auditory Brainstem Implant, a Meta-analysis. *Otol Neurotol*. 39(4), 428-437. doi:10.1097/mao.0000000000001727.

Walker, E., McCreery, R., Spratford, M., Roush, P. (2016). Children with Auditory Neuropathy Spectrum Disorder Fitted with Hearing Aids Applying the American Academy of Audiology Pediatric Amplification Guideline: Current Practice and Outcomes. *J Am Acad Audiol*. 27(3), 204-218. doi:10.3766/jaaa.15050.

Walton, J., Gibson, W.P., Sanli, H., Prelog, K. (2008). Predicting cochlear implant outcomes in children with auditory neuropathy. *Otol Neurotol*. 29(3), 302-309. doi:10.1097/MAO.0b013e318164d0f6.

Wang, H., Wang, L., Yang, J., Yin, L., Lan, L., Li, J., Zhang, Q., Wang, D., Guan, J., Wang, Q. (2019). Phenotype prediction of Mohr-Tranebjaerg syndrome (MTS) by genetic analysis and initial auditory neuropathy. *BMC Med Genet*. 20(1), 11. doi:10.1186/s12881-018-0741-3.

Wolfe, J., 2020. Cochlear Implants: Audiologic Management and Considerations for Implantable Hearing Devices. Plural Publishing Inc., San Diego.

Yamazaki, H., Leigh, J., Briggs, R., Naito, Y. (2015). Usefulness of MRI and EABR Testing for Predicting CI Outcomes Immediately After Cochlear Implantation in Cases With Cochlear Nerve Deficiency. *Otol Neurotol*. 36(6), 977-984. doi:10.1097/mao.0000000000000721.

Yoshinaga-Itano, C., Sedey, A.L., Coulter, D.K., Mehl, A.L. (1998). Language of early- and later-identified children with hearing loss. *Pediatrics*. 102(5), 1161-1171. doi:10.1542/peds.102.5.1161.

Zhang, Z., Xu, X., Ni, H. (2013). Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study. *Crit Care*. 17(1), R2. doi:10.1186/cc11919.

Chapter 2

Title: Predictors of Intervention Outcomes in Children with Auditory Neuropathy Spectrum Disorder

Short Title: Open-set Speech Perception Performance in Children with ANSD

Authors: Zahra Jafari,[1] Elizabeth M. Fitzpatrick,[1,2] David R. Schramm,[3,4] Isabelle Rouillon,[5] Amineh Koravand[1]

[1]Audiology and Speech-Language Pathology Program, University of Ottawa, Ottawa, Ontario, Canada.

[2]Child Hearing Laboratory, CHEO Research Institute, Ottawa, Ontario, Canada.

[3]Department of Otolaryngology-Head and Neck Surgery, University of Ottawa, Ottawa, Ontario, Canada.

[4]Department of Otolaryngology-Head and Neck Surgery, The Ottawa Hospital, Ottawa, Ontario, Canada.

[5]Department of Pediatric Otolaryngology, AP-HP, Hôpital Necker-Enfants Malades, Paris, France.

Corresponding Author: Amineh Koravand

Jafari Z, Fitzpatrick EM, Schramm DR, Rouillon I, Koravand A. Predictors of Intervention Outcomes in Children with Auditory Neuropathy Spectrum Disorder. *Submitted*. Under review.

Abstract

Introduction: Existing evidence supports the benefits of cochlear implants/hearing aids (CI/HA) for children with auditory neuropathy spectrum disorder (ANSD). However, evidence is limited regarding factors with predictive value for intervention outcomes in children with ANSD.

Methods: The records of 38 children with ANSD using CIs (71%) and/or HAs identified at the Children's Hospital of Eastern Ontario (Ottawa, Canada) were reviewed.

Results: In children with congenital or early-onset hearing loss (HL), the mean age at HL diagnosis, HA fitting, and CI activation was 5.68, 18.43, and 29.43 months, respectively. A significant difference was observed between ages at HL diagnosis and CI activation ($p < 0.001$). Younger age at HL diagnosis and CI activation and longer duration of follow-up with CI/HA were significantly associated with better open-set speech perception outcomes (i.e., the scores on Phonetically Balanced Kindergarten Test-Words and Phonemes and Hearing in Noise Test in quiet and noise conditions). In an analysis using a Forward Linear multiple Regression Model, a longer follow-up period and bilateral amplification showed prognostic value for higher speech perception test scores.

Conclusions: In children with ANSD, a longer follow-up with CI/HA and bilateral amplification have prognostic value for better intervention outcomes. Taking into account the role of other contributing factors could provide a stronger estimate of variables with predictive value for hearing intervention outcomes.

Keywords: Auditory neuropathy spectrum disorder; Cochlear implant; Hearing aid; Speech perception; Intervention outcome; Bilateral amplification; Follow-up period; Prognostic value.

Introduction

Auditory neuropathy spectrum disorder (ANSD) is observed in 4% to 5% of all degrees of hearing loss, and 10% to 15% of school-age children with severe to profound sensorineural hearing loss (SNHL) (Bielecki et al., 2012; Mittal et al., 2012). ANSD is characterized by hearing impairment despite normally functioning outer hair cells (OHCs) (Shearer and Hansen, 2019). In clinical audiology, ANSD is characterized by normal otoacoustic emissions (OAE) and/or cochlear microphonics (CM), indicating normal cochlear function, accompanied by an abnormal transmission of auditory signals from cochlear synapses to the brain as evidenced by absent or severely abnormal auditory brainstem responses (ABRs) (Rance and Starr, 2015; Shearer and Hansen, 2019). The lesion site causing ANSD may vary from the presynaptic site of release of glutamate in the inner hair cells (IHCs) to the cochlear synapse, the postsynaptic site of neurotransmitter stimulation, the site of initiation of the excitatory postsynaptic potential (EPSP) at the terminal dendrite, or sites along the spiral ganglion, which affect auditory signal transmission along the auditory nerve to the brain (Rance and Starr, 2015; Shearer and Hansen, 2019). In ANSD, deficiency in neural transmission (due to a reduced number of activated auditory nerve fibers or deafferentation) and/or neural dyssynchrony (due to progressive demyelination) are the two basic mechanisms that contribute to the disruption of neural activity and temporal resolution deficits at the auditory brainstem level (Rance and Starr, 2011; Starr and Rance, 2015). Temporal resolution is the ability to perceive changes in stimuli over time, for example, to detect a brief gap between two sounds or amplitude fluctuations in a continuous sound (Rance, 2005). Individuals with ANSD typically show difficulty with the temporal processing of sound resulting in impaired speech perception, especially in background noise (Hood, 2021; Rance, 2005).

The etiology of ANSD is complex and can broadly be classified into acquired and genetic factors (Manchaiah et al., 2011). A wide range of acquired factors, such as perinatal conditions (e.g., hyperbilirubinemia, hypoxia, preterm birth, low birth weight, and mechanical ventilation), neurometabolic disorders, immune disorders, and ototoxic drug exposure may contribute to ANSD (Hall, 2015; James et al., 2020; Manchaiah et al., 2011). More than 40% of patients with ANSD have a genetic predisposition (Manchaiah et al., 2011; Saidia et al., 2023), including autosomal recessive (OTOF, PJVK), autosomal dominant (OPA1, MPZ, ATP1A3, SLC17A8, DIAPH3), X-linked (AIFM1), and maternally inherited mitochondrial mutations (Huang et al., 2022; Saidia et al., 2023).

Intervention and management for ANSD are challenging and require a team approach including parental education about ANSD management (Hall, 2015; Wolfe, 2020). Hearing technology interventions for ANSD vary according to individual cases due to the extent of the lesion and disease severity (Myers and Nicholson, 2021). The most common auditory options include maximizing the signal-to-noise ratio (SNR) to enhance speech perception in noise or amplifying sound with hearing aids (HAs) or cochlear implants (CIs) (Starr and Rance, 2015; Wolfe, 2020). Conventional HAs may be used to amplify the acoustic signal and improve speech audibility in ANSD. The American Academy of Audiology (AAA) Pediatric Amplification Guidelines recommend a HA trial for children with reliable, permanent HL that interferes with speech perception at conversational levels (Walker et al., 2016). However, HAs may not be an appropriate option for many patients with ANSD as making sounds louder does not improve the processing of auditory temporal cues (Berlin et al., 2010; Ching et al., 2013a). Cochlear implantation has revolutionized the care for individuals with severe to profound hearing loss (HL). Given that the perception of auditory information is largely based on temporal processing, which

can be successfully transmitted by only a few electrodes (Kuchta, 2007), CIs are the standard of care for many patients with ANSD (Shearer and Hansen, 2019). The CI bypasses the lesion site (i.e., IHCs and cochlear synapses) and directly stimulates the spiral ganglion neurons. Further, compared to acoustic stimulation, electric stimulation is superior in stimulating and synchronizing auditory nerve fibers (Shearer and Hansen, 2019), which enhances neural synchrony and allows the development of fundamental speech and hearing skills (Chaudhry et al., 2020).

Similar to children with SNHL, better outcomes in children with ANSD are associated with receiving hearing interventions (CIs or HAs) before three years of age (Ching et al., 2013a; Ching et al., 2013b; Niparko et al., 2010). According to the literature, various factors contribute to intervention outcomes such as the lesion site, age at HL diagnosis, additional disabilities and/or medical comorbidities (ADs/MCs), age at CI activation, using one or two CIs, length of follow-up with CI/HA, and sex (Bo et al., 2022; Cupples et al., 2018; Myers and Nicholson, 2021; Peng et al., 2017; Rajput et al., 2019; Rance and Starr, 2015; Vesseur et al., 2018). Although the majority of children with ANSD may attain speech, language, and communication abilities equivalent to their peers with SNHL (Madden et al., 2002; Mason et al., 2003; Rance and Barker, 2009; Santarelli et al., 2015; Shallop, 2002; Teagle et al., 2010; Zeng and Liu, 2006), a subgroup of children with cochlear nerve deficiency (CND) may attain minimal benefits from CIs and show limited progress in developing functionally useful auditory communication skills (Gibson and Sanli, 2007; Roush et al., 2011; Teagle et al., 2010). While existing evidence demonstrates the benefits of HAs and CIs (Bo et al., 2022; Myers and Nicholson, 2021; Peng et al., 2017; Vesseur et al., 2018), factors with prognostic value for intervention outcomes have been less studied. The objectives of the present study were to determine the relationship between open-set speech perception outcomes and ages at HL diagnosis, CI activation, and length of follow-up with CI/HA

and to identify factors that have predictive value for open-set speech perception outcomes. We hypothesized that post-intervention outcomes would be affected positively by age at CI activation, using bilateral amplification, and the length of follow-up with CI/HA; and negatively by ADs/MCs and admission to the neonatal intensive care unit (NICU).

Methods

Participants

This retrospective chart review was conducted at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Canada in 2023. Chart review and data extraction at CHEO was approved by both CHEO REB (Protocol No: 22/83X) (Appendix I) and the University of Ottawa Office of Research Ethics and Integrity (Ethics File Number # H-11-22-8149) (Appendix II). The records of all children diagnosed with ANSD (n = 38) using CIs and/or HAs between 2000 and 2022 were included in this study. The ANSD diagnosis was based on inconsistency in audiologic findings in the clinical setting, consisting of present OAEs and/or CMs, absent or severely abnormal ABR, and various degrees of SNHL irrespective of present OAEs and/or CMs (Hayes and Sininger, 2008). Of the 27 children with CIs, MRI reports were available for 24. Only one child was identified as CND (bilateral hypoplasia). Children with less than six-month use of HAs and/or CIs were not included in the study. For data extraction, both electronic and paper records were reviewed by two research assistants independent of the authors. The list of data extracted for this study was: age, HL characteristics (i.e., degree of HL, the onset of HL, age of HL diagnosis), CI/HA characteristics (i.e., type of CIs or HAs, the use of one or two CIs/HAs, age at HA fitting, and age at CI activation), medical conditions (i.e., ADs/MCs, NICU history, and preterm birth), results of open-set speech perception scores (i.e., outcome measures), and the length of follow-up with CI/HA.

Outcome Measures

The outcome measures in this study were the tests of open-set speech recognition consisting of the Phonetically Balanced Kindergarten (PBK) test using both monosyllabic word (PBK-W) and phoneme (PBK-P) speech materials, and the Hearing in Noise Test for children (HINT-C) using sentence materials in both quiet and noise conditions. For the PBK test, recorded speech materials including 25 monosyllabic words (PBK-W) and 80 phonemes (PBK-P) were presented at 60 dB SPL (He et al., 2015). The HINT test sentences were administered in both quiet and noise conditions with speech-shaped noise at 10 and 5 dB SNRs (HINT-10 and HINT-5, respectively) at 60 dB SPL (Eisenberg et al., 2016). All speech perception tests were administered in a sound booth in the clinical setting. In the chart review, the length of follow-up with CI/HA was defined based on the most recent follow-up session with speech perception test results reported. Therefore, this measure refers to the difference between the date of HA fitting (for children using HAs) or the date of CI activation (the first CI in children with CIs), and the date of test administration.

Statistical Analysis

Statistical analysis was conducted with SPSS Statistics 26.0 at a significance level of 0.05 or better. Univariate analysis of variance test was used to compare age at HL diagnosis, age at HAs, and age at CI activation in children with and without a history of NICU admission, preterm birth, or ADs/MCs. The Spearman's rank correlation coefficient test was used to assess the correlation between outcome measures (i.e., speech perception test scores) and age at HL diagnosis, age at CI activation, and the length of follow-up with CI/HA. A regression of speech perception outcome measures with age as a single independent variable was conducted to ensure

that the correlations presented in Figure 1 were not solely influenced by the year of birth of a few older children (i.e., the potential impact of birth year on the results). As the regression did not yield significance ($p \geq 0.136$), it was concluded that the year of birth had no significant impact on the reported relationships.

To identify variables with prognostic value for intervention outcomes, a Forward Linear multiple Regression Model was employed. The variables included were age at HL diagnosis, age at HA fitting, age at CI activation, length of follow-up with CI/HA, onset of HL, use of bilateral amplification, history of NICU admission, preterm birth, ADs/MCs, and sex (Appendix III).

Results

The present retrospective study reports the results of 38 children with ANSD, including 24 (63.2%) males and 14 (36.8%) females aged 5 to 18 years old. The HL onset was reported as congenital or early-onset, late-onset, or unknown in 23 (60.50%), 9 (23.70%), and 6 (15.80%) children, respectively. Table 1 summarizes the demographic and audiologic characteristics of children included in this study, consisting of case number (27 with CIs and 11 with HAs), sex, device type/intervention (CIs or HAs), age at HL diagnosis (months), age at HA fitting (months), age at CI activation (months), the length of follow-up with CI/HA (months), preoperative HL degree, ADs/MCs, and history of preterm birth (PB) and NICU admission.

Ages at HL Diagnosis, HAs, and CIs

Table 2 presents the mean, median, standard deviation, and range of ages at HL diagnosis, HA fitting, and CI activation based on the onset of HL, i.e., congenital or early-onset, late-onset, and unknown. In comparing the three ages in children with congenital or early-onset hearing loss ($F= 29.52$, $p < 0.001$, partial $\eta^2 = 0.557$, and power = 1.00), no significant difference was observed

between age at HL diagnosis and age at HA fitting ($p = 0.061$). However, the difference between age at HL diagnosis and age at CI activation was significant ($p < 0.001$).

Impact of NICU Admission, Preterm Birth, and ADs/MCs

Of the total 38 children with ANSD, 15 (39.47%) had a history of NICU admission, 18 (47.36%) had a history of PB, and 23 (60.52%) had ADs/MCs. Table 3 demonstrates the mean, median, and SD of age at HL (months), age at HAs (months), and age at CIs (months) in children with or without a history of NICU, PB, or ADs/MCs. There was no significant difference between children with or without a history of NICU admission ($p \geq 0.152$), PB ($p \geq 0.676$), or ADs/MCs ($p \geq 0.628$) in age at HL diagnosis, age at HAs, and age at CI activation.

Open-set Speech Perception Test Scores

Table 4 exhibits the mean, median, SD, and range of test scores for PBK-W, PBK-P, HINT in quiet, and HINT in noise with 10 and 5 dB SNRs. The average length of follow-up with CI/HA was 98.77 months (SD = 57.57, median = 101.50, range = 6.00 to 198.00), including 105.72 months (SD = 61.34, median = 123.00, range = 6.00 to 198.00) for children with CIs and 87.54 months (SD = 48.67, median = 91.00, range = 6.00 to 168.00) for children with HAs.

Factors Correlating to Speech Perception Outcomes

Age at HL diagnosis showed a significant negative correlation with PBK-P scores ($r = -0.582$, $p = 0.023$, $n = 14$) (Figure 1A).

Age at CI activation showed a significant negative correlation with PBK-W scores ($r = -0.634$, $p = 0.011$, $n = 20$), and HINT-10 ($r = -0.675$, $p = 0.039$, $n = 13$) and HINT-5 ($r = -0.606$, $p = 0.048$, $n = 13$) sentence test scores (Figures 1B, 1C, and 1D, respectively).

A significant positive correlation was found between the length of follow-up with CI/HA and open-set speech recognition using the PBK-W test ($r = 0.512$, $p = 0.021$, $n = 20$), PBK-P test ($r = 0.702$, $p = 0.005$, $n = 14$), and HINT test in quiet ($r = 0.695$, $p = 0.009$, $n = 13$) (Figure 2).

Predictors of Intervention Outcomes

A Forward Linear multiple Regression Model, including 10 potential contributors, was used to determine factors with predictive value for intervention outcomes. Table 5 summarizes the results of statistical analyses, including the variables identified with a significant prognostic value for intervention outcomes, regression coefficient (R square), F and p magnitudes, and standardized coefficient Beta. For example, among the list of potential contributors included in the regression model, "the length of follow-up with CI/HA" was the only factor that showed a significant contribution ($r = 0.448$, $p = 0.005$) to the PBK-W results. Based on the regression coefficient, it could be interpreted that 44.80% of the outcome (i.e., PBK-W score) was explained by the follow-up period. In addition, the positive magnitude of the beta value (0.66) was indicative of improved speech perception performance with increased length of the intervention follow-up. The same results were obtained for the PBK-P test (regression coefficient = 62.70%), corroborating the predictive value of the length of follow-up with CI/HA for speech perception outcomes. However, for the HINT test in both quiet and noise (10 and 5 dB SNRs) conditions, "bilateral amplification" was the factor that showed significant prognostic value. According to the regression coefficient values, bilateral amplification explained 60.50% of the HINT score in quiet, 41.80% with 10dB SNR, and 77.20% with 5dB SNR. Likewise, the positive magnitude of the beta values (0.778, 0.695, and 0.850) suggested improved speech perception performance with increased follow-up duration.

Discussion

The primary objective of the present retrospective study was to investigate the factors that have a significant impact on post-intervention speech perception outcomes in children with ANSD. In this study: 1) There was a significant difference between age at HL diagnosis and age at CI activation. A history of NICU admission, PB, and ADs/MCs had no significant impact on these ages. 2) Open-set speech perception test scores were positively associated with lower age at HL diagnosis and age at CI activation, and longer follow-up with CI/HA. 3) A longer follow-up period demonstrated prognostic value for better PBK test scores (using both word and phoneme speech materials), and bilateral amplification showed a predictive value for higher HINT test scores in both quiet and noise conditions. The model identified no other predictors that could add to the impact of the follow-up period and bilateral amplification. In the following paragraphs, the main findings are discussed.

Age at HL Diagnosis and Hearing Interventions and the Impact of Risk Factors

Table 6 summarizes the age at HL diagnosis (Ching et al., 2013a; Ching et al., 2013b; Fitzpatrick et al., 2011; Harrison and Roush, 1996; Jafari et al., 2007; Kittrell and Arjmand, 1997; le Roux et al., 2016; Ozcebe et al., 2005; Prendergast et al., 2002), age at HA fitting (Ching et al., 2013a; Ching et al., 2013b; Fitzpatrick et al., 2011; Harrison and Roush, 1996; Jafari et al., 2007; Kittrell and Arjmand, 1997; Ozcebe et al., 2005; Prendergast et al., 2002), and age at CIs (Budenz et al., 2013; Ching et al., 2013a; Ching et al., 2013b; Fitzpatrick et al., 2011; Kontorinis et al., 2014; le Roux et al., 2016) reported in similar studies on children with ANSD (Budenz et al., 2013; Kontorinis et al., 2014) or SNHL (Budenz et al., 2013; Fitzpatrick et al., 2011; Harrison and Roush, 1996; Jafari et al., 2007; Kittrell and Arjmand, 1997; le Roux et al., 2016; Ozcebe et al., 2005; Prendergast et al., 2002). In our study, these three ages in children with congenital or early-onset

HL (5.68, 18.43, and 29.43 months) were comparable to most previous studies, except for Ching et al. studies (2013) on children with SNHL or ANSD who were diagnosed with HL and received CIs/HAs before three years of age in an EHDI program (Ching et al., 2013a; Ching et al., 2013b). In all but one study (Budenz et al., 2013), a fraction of children had ADs/MCs. The frequency of ADs/MCs in our study was higher than the values reported in past studies, and this factor had no significant impact on the three ages reported. In the Harrison and Roush (1996) study on children with SNHL, higher degrees of HL (severe to profound vs. mild to moderate) and the presence of ADs/MCs were associated with earlier ages at HL diagnosis and HA fitting. Our findings should be interpreted with caution due to a low sample size of children with ANSD, with an increased rate of ADs/MCs compared to previous reports, suggesting the need for further studies in the future.

Early sensory deprivation can cause significant brain reorganization resulting from compensatory and cross-modal neural plasticity (Kupers and Ptito, 2014; Merabet and Pascual-Leone, 2010). According to neurodevelopmental studies, the childhood period below age 4 years, especially the first two years of life, is the most sensitive period for spoken language development, when the brain, including the central auditory nervous system, exhibits maximum plasticity (Kral and Sharma, 2012; Sharma and Campbell, 2011). Since the beginning of early hearing detection and intervention (EHDI) programs, extensive evidence in ANSD supports the benefits of early identification and, more importantly, early intervention with HAs and/or CIs (Ambrose et al., 2014; Cowan et al., 2018; Cupples et al., 2018; Tomblin et al., 2015; Wolfe, 2020). For more than half a century, the Joint Committee on Infant Hearing (JCIH) has advocated for EHDI (Myers and Nicholson, 2021). It is well-accepted that the lack of auditory stimulation during the critical period of spoken language development results in delays in auditory, speech, language, social, emotional,

and cognitive development (Dillon et al., 2013; Robertson et al., 2009; Yoshinaga-Itano, 1999; Yoshinaga-Itano et al., 1998). Thus, identifying demographic, socioeconomic, and clinical factors (i.e., facilitators and barriers) that affect EHDI is the key. Findings of studies indicate that in addition to audiologic (e.g., progressive hearing loss) or complex medical conditions (Fitzpatrick et al., 2011), other factors such as socioeconomic status, parental education (Omar et al., 2022a; Omar et al., 2022b), race/ethnicity, primary language (Kothari et al., 2015; Lieu et al., 2020; Zhang et al., 2020), and the burden of distance for access to CI (Cheung et al., 2023; Noblitt et al., 2018) can significantly influence early intervention and aural rehabilitation programs in the pediatric population.

Correlation Between Speech Perception Scores with Age at HL Diagnosis, Age at CIs, and the Follow-up Period

In the present study, open-set speech perception test scores were negatively associated with ages at HL diagnosis and CI activation and positively associated with the length of follow-up with CI/HA. Our findings on the contribution of earlier ages at HL diagnosis and CI activation, and a longer follow-up period to speech perception performance are aligned with past evidence of the impact of auditory deprivation and long-term use of hearing amplification on spoken language development in children with congenital or early onset HL. For example, in two studies (Daneshi et al., 2018; Liu et al., 2014), children with ANSD who received CIs before 24 months of age achieved higher scores in the Categories of Auditory Perception (CAP) test and Speech Intelligibility Rating (SIR) test compared to children who were implanted after 24 months of age. In a systematic review with a narrative synthesis of evidence (Bruijnzeel et al., 2016) on implanted children with follow-up periods ranging from 6 months to 9 years, cochlear implantation before

24 months was found to be beneficial according to the scores of PBK and consonant-nucleus-consonant (CNC) tests. In addition, implantation before 12 months was associated with better speech production (using Diagnostic Evaluation of Articulation and Phonology and Infant-Toddler Meaningful Auditory Integration Scale [IT-MAIS]), auditory performance (the CAP-II score), and receptive language scores (based on the Preschool Language Scale combined with oral and written language skills and Peabody Picture Vocabulary Test). In another similar review, language outcomes for children implanted after 12 months decreased with the increased age of implantation (Ruben, 2018). In a study investigating cortical maturation, measured by P1 cortical auditory evoked potential (CAEP) latency, P1 CAEP latency was significantly correlated with children's scores on the IT-MAIS. P1 CAEP responses were present in all children after implantation (Cardon and Sharma, 2013), compared to previous studies suggesting that only 50 (Rance et al., 2002) to 75% (Sharma et al., 2011) of ANSD children with HAs showed CAEP responses. It was concluded that children fitted with CIs under two years of age were more likely to show age-appropriate CAEP responses within six months after implantation, suggesting a possible sensitive period for cortical auditory development in ANSD (Cardon and Sharma, 2013).

The importance of early HL diagnosis and early hearing intervention is associated with the fact that the brain has high synaptic plasticity during childhood that progressively declines with age. This decline results from developmental mechanisms such as attenuated synaptic conductivity and the maturation of inhibitory neurons (Kolb and Muhammad, 2014). This age-related neural development shapes sensory object discrimination (Kral et al., 2019). In addition, brain development is highly modulated by sensory inputs and profoundly reshaped by the lack of one sensory modality (Bavelier and Neville, 2002; Merabet and Pascual-Leone, 2010). According to

MRI studies, early auditory deprivation leads to reduced white matter volume and integrity in the primary and secondary auditory cortex and spoken-language brain areas (Hribar et al., 2014; Karns et al., 2017). The extent of structural neuroplasticity is an index of poor speech-language performance in late CI recipients (Simon et al., 2020). In addition, auditory processing deficits due to functional intra-modal changes (e.g., the reduction of tonotopy, dynamic range, temporal resolution, and sensitivity to binaural cues) occur, which severely degrade the acuity of the auditory signal perceived (Kral et al., 2019; Kral et al., 2017). The findings of studies reviewed here underscore the crucial role of the sensitive period of auditory and spoken language development; a time limit of below 4 years, especially within the first two years of life (Kral and Sharma, 2012; Sharma and Campbell, 2011; Shirvani et al., 2016), in which the central auditory system is highly plastic, and CI surgery could result in optimal outcomes (Kral et al., 2019).

Factors with Prognostic Value for Speech Perception Outcomes

We used a Forward Linear multiple Regression Model to determine the factors showing significant prognostic value for post-intervention outcomes. Among the 10 variables included in the regression model (i.e., age of HL diagnosis, age at fitting HAs, age at CI activation, follow-up period, the onset of HL, using one or two CIs, NICU history, preterm birth, additional disabilities/medical comorbidities, and sex), a longer follow-up with CI/HA and bilateral amplification were the two factors that showed prognostic value for better speech perception outcomes (i.e., PBK and HINT test scores). The regression model identified no additional factors that could add to the predictive value of follow-up duration and bilateral amplification. Limited studies have reported the use of statistical models in identifying predictors of intervention outcomes. In a prospective study by Ching et al. (2013b) on 451 children in Australia with HL

(30% with CIs, 10% with ANSD), age at CI activation, absence of ADs, higher maternal education, and female sex were reported as predictors for post-CI outcomes. In a subsequent report by the same research group on language outcomes (Ching et al., 2017), the benefit of early intervention for language development increased as hearing loss increased. Children who received amplification at age 24 months had lower language scores than those fitted at 3 months, and children who received CIs at 24 months had lower language scores than those implanted at 6 months. In a retrospective study by le Roux et al. (2016) on 301 children with CIs (3.5% with ANSD) from five CI programs in South Africa, using two CIs, ADs/MCs, mainstream education, and ethnicities other than Caucasian contributed to post-CI outcomes.

The output of the regression model depends on the sample size and the number of factors included in the model. In our chart review, the study population included children with ANSD, and we did not access further relevant information in children's records (e.g., socioeconomic status, maternal education, and mode of communication at home), which might have contributed to the outcomes. An interesting finding in the present study was the significant contribution of the length of follow-up with CI/HA to the PBK (word and phoneme) test scores and using bilateral amplification to HINT (in quiet and with 10dB and 5dB SNRs) test scores. The findings for the PBK test may indicate that in the long term, the length of follow-up with CI/HA is a stronger factor contributing to outcomes than other influential variables such as age at CI activation and ADs/MCs. The findings for the HINT test might be associated with the HINT test's higher complexity due to the use of sentence materials and competing noise.

The strength of this study was in reporting the role of several key contributing factors to the open-set speech perception test scores in a sample of children identified with ANSD. These

findings could be useful for health-related professionals in decision-making for EHDI, as well as in counseling or guiding parents of children with HL, especially those who are candidates for CIs. The study also had several limitations including a lack of a control group, genetic background, and information about other potential contributors (e.g., maternal education, mode of communication at home, socioeconomic status), as well as low sample size and missing data on speech perception outcomes (i.e., not all children had all test scores available), which could affect the findings, and their likely impact should be taken into account.

Conclusions

In this retrospective study, we reviewed three critical ages in providing aural rehabilitation services for children with ANSD, the impact of ADs/MCs on these ages, and the factors contributing to open-set speech perception outcomes. More than two-thirds of children with ANSD used CIs. In children with congenital or early-onset HL, a significant difference was identified between age at HL diagnosis and age at CI activation, and factors such as NICU admission, PB, or ADs/MCs had no significant impact on these ages. However, lower ages at HL diagnosis and CI activation, and longer follow-up with CI/HA were significantly associated with better open-set speech perception outcomes, and longer follow-up duration and bilateral amplification showed prognostic value for speech perception outcomes. Our findings suggest that in children with ANSD, lower ages of HL diagnosis and CI activation, long-term amplification use, and bilateral amplification are associated with better intervention outcomes. Prospective studies and consideration of other potential contributors (i.e., demographics, genetics, and cognitive factors) may help provide a better estimate of the factors affecting ANSD intervention outcomes.

Conflict of interest: The authors disclose no competing interests.

Acknowledgment: This article was part of a Ph.D. dissertation project in Rehabilitation Sciences, the Audiology and Speech-Language Pathology Program, approved by Ottawa University, Faculty of Health Sciences, School of Rehabilitation Sciences. We appreciate Chantal Lessard (Coordinator and Professional Practice Leader at CHEO) and JoAnne Whittingham (Research Coordinator at CHEO) who helped with ethical approval and access to data, and Ines Telmat and Jennifer Ti Nguyen who assisted with data extraction.

Funding: This research was offered funding support from the Ontario Graduate Scholarship (OGS) and the Queen Elizabeth II Scholarships in Science and Technology (QEII-GSST).

Author Contributions: ZJ and AK conceptualized the study, ZJ conducted chart review, data extraction, and data analyses, and wrote the first draft of the manuscript. All authors read and approved the publication of the final manuscript. AK provided project leadership.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author (AK).

References

Ambrose, S.E., Unflat Berry, L.M., Walker, E.A., Harrison, M., Oleson, J., Moeller, M.P. (2014). Speech sound production in 2-year-olds who are hard of hearing. *Am J Speech Lang Pathol*. 23(2), 91-104. doi:10.1044/2014_ajslp-13-0039.

Bavelier, D., Neville, H.J. (2002). Cross-modal plasticity: Where and how? *Nat Rev Neurosci*. 3(6), 443-452. doi:10.1038/nrn848.

Berlin, C.I., Hood, L.J., Morlet, T., Wilensky, D., Li, L., Mattingly, K.R., Taylor-Jeanfreau, J., Keats, B.J., John, P.S., Montgomery, E., Shallop, J.K., Russell, B.A., Frisch, S.A. (2010). Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-

synchrony (auditory neuropathy spectrum disorder). *Int J Audiol*. 49(1), 30-43. doi:10.3109/14992020903160892.

Bielecki, I., Horbulewicz, A., Wolan, T. (2012). Prevalence and risk factors for auditory neuropathy spectrum disorder in a screened newborn population at risk for hearing loss. *Int J Pediatr Otorhinolaryngol*. 76(11), 1668-1670. doi:10.1016/j.ijporl.2012.08.001.

Bo, D., Huang, Y., Wang, B., Lu, P., Chen, W.X., Xu, Z.M. (2022). Auditory and Speech Outcomes of Cochlear Implantation in Children With Auditory Neuropathy Spectrum Disorder: A Systematic Review and Meta-Analysis. *Ann Otol Rhinol Laryngol*, 34894221092201. doi:10.1177/00034894221092201.

Bruijnzeel, H., Ziylan, F., Stegeman, I., Topsakal, V., Grolman, W. (2016). A Systematic Review to Define the Speech and Language Benefit of Early (<12 Months) Pediatric Cochlear Implantation. *Audiol Neurootol*. 21(2), 113-126. doi:10.1159/000443363.

Budenz, C.L., Telian, S.A., Arnedt, C., Starr, K., Arts, H.A., El-Kashlan, H.K., Zwolan, T.A. (2013). Outcomes of cochlear implantation in children with isolated auditory neuropathy versus cochlear hearing loss. *Otol Neurotol*. 34(3), 477-483. doi:10.1097/MAO.0b013e3182877741.

Cardon, G., Sharma, A. (2013). Central auditory maturation and behavioral outcome in children with auditory neuropathy spectrum disorder who use cochlear implants. *Int J Audiol*. 52(9), 577-586. doi:10.3109/14992027.2013.799786.

Chaudhry, D., Chaudhry, A., Muzaffar, J., Monksfield, P., Bance, M. (2020). Cochlear Implantation Outcomes in Post Synaptic Auditory Neuropathies: A Systematic Review and Narrative Synthesis. *J Int Adv Otol*. 16(3), 411-431. doi:10.5152/iao.2020.9035.

Cheung, L.L., Fowler, A., Hassarati, R.T., Birman, C.S. (2023). Distance and Socieoeconomic Status as Barriers to Cochlear Implantation. *Otol Neurotol*. 44(2), 134-140. doi:10.1097/mao.0000000000003765.

Ching, T.Y., Day, J., Dillon, H., Gardner-Berry, K., Hou, S., Seeto, M., Wong, A., Zhang, V. (2013a). Impact of the presence of auditory neuropathy spectrum disorder (ANSD) on outcomes of children at three years of age. *Int J Audiol*. 52 Suppl 2(0 2), S55-64. doi:10.3109/14992027.2013.796532.

Ching, T.Y., Dillon, H., Marnane, V., Hou, S., Day, J., Seeto, M., Crowe, K., Street, L., Thomson, J., Van Buynder, P., Zhang, V., Wong, A., Burns, L., Flynn, C., Cupples, L., Cowan, R.S., Leigh, G., Sjahalam-King, J., Yeh, A. (2013b). Outcomes of early- and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear Hear*. 34(5), 535-552. doi:10.1097/AUD.0b013e3182857718.

Ching, T.Y.C., Dillon, H., Button, L., Seeto, M., Van Buynder, P., Marnane, V., Cupples, L., Leigh, G. (2017). Age at Intervention for Permanent Hearing Loss and 5-Year Language Outcomes. *Pediatrics*. 140(3). doi:10.1542/peds.2016-4274.

Cowan, R.S.C., Edwards, B., Ching, T.Y.C. (2018). Longitudinal outcomes of children with hearing impairment (LOCHI): 5-year data. *Int J Audiol*. 57(sup2), S1-s2. doi:10.1080/14992027.2018.1458703.

Cupples, L., Ching, T.Y.C., Button, L., Leigh, G., Marnane, V., Whitfield, J., Gunnourie, M., Martin, L. (2018). Language and speech outcomes of children with hearing loss and additional disabilities: identifying the variables that influence performance at five years of age. *Int J Audiol*. 57(sup2), S93-s104. doi:10.1080/14992027.2016.1228127.

Daneshi, A., Mirsalehi, M., Hashemi, S.B., Ajalloueyan, M., Rajati, M., Ghasemi, M.M., Emamdjomeh, H., Asghari, A., Mohammadi, S., Mohseni, M., Mohebbi, S., Farhadi, M. (2018). Cochlear implantation in children with auditory neuropathy spectrum disorder: A multicenter study on auditory performance and speech production outcomes. *Int J Pediatr Otorhinolaryngol*. 108, 12-16. doi:10.1016/j.ijporl.2018.02.004.

Dillon, H., Cowan, R., Ching, T.Y. (2013). Longitudinal outcomes of children with hearing impairment (LOCHI). *Int J Audiol*. 52 Suppl 2, S2-3. doi:10.3109/14992027.2013.866448

Eisenberg, L.S., Fisher, L.M., Johnson, K.C., Ganguly, D.H., Grace, T., Niparko, J.K. (2016). Sentence Recognition in Quiet and Noise by Pediatric Cochlear Implant Users: Relationships to Spoken Language. *Otol Neurotol*. 37(2), e75-81. doi:10.1097/mao.0000000000000910.

Fitzpatrick, E.M., Johnson, E., Durieux-Smith, A. (2011). Exploring factors that affect the age of cochlear implantation in children. *Int J Pediatr Otorhinolaryngol*. 75(9), 1082-1087. doi:10.1016/j.ijporl.2011.05.018.

Gibson, W.P., Sanli, H. (2007). Auditory neuropathy: an update. *Ear Hear*. 28(2 Suppl), 102s-106s. doi:10.1097/AUD.0b013e3180315392.

Hall, J., 2015. eHandbook of Auditory Evoked Responses: Principles, Procedures & Protocols. . Pearson Education, Inc.

Harrison, M., Roush, J. (1996). Age of suspicion, identification, and intervention for infants and young children with hearing loss: a national study. *Ear Hear*. 17(1), 55-62. doi:10.1097/00003446-199602000-00007.

Hayes, D., Sininger, Y., 2008. Guidelines for Identification and Management of Infants and Young Children with Auditory Neuropathy Spectrum Disorder, NHS 2008, Como, Italy.

He, S., Grose, J.H., Teagle, H.F., Woodard, J., Park, L.R., Hatch, D.R., Roush, P., Buchman, C.A. (2015). Acoustically evoked auditory change complex in children with auditory neuropathy spectrum disorder: a potential objective tool for identifying cochlear implant candidates. *Ear Hear*. 36(3), 289-301. doi:10.1097/aud.0000000000000119.

Hood, L.J. (2021). Auditory Neuropathy/Auditory Synaptopathy. *Otolaryngol Clin North Am*. 54(6), 1093-1100. doi:10.1016/j.otc.2021.07.004.

Hribar, M., Suput, D., Carvalho, A.A., Battelino, S., Vovk, A. (2014). Structural alterations of brain grey and white matter in early deaf adults. *Hear Res*. 318, 1-10. doi:10.1016/j.heares.2014.09.008.

Huang, Y., Yang, J., Duan, M. (2022). Auditory neuropathy: from etiology to management. *Curr Opin Otolaryngol Head Neck Surg*. 30(5), 332-338. doi:10.1097/moo.0000000000000829

Jafari, Z., Malayeri, S., Ashayeri, H. (2007). The ages of suspicion, diagnosis, amplification, and intervention in deaf children. *Int J Pediatr Otorhinolaryngol*. 71(1), 35-40. doi:10.1016/j.ijporl.2006.08.014.

James, A.L., Osborn, H.A., Osman, H., Papaioannou, V., Gordon, K.A. (2020). The limitation of risk factors as a means of prognostication in auditory neuropathy spectrum disorder of perinatal onset. *Int J Pediatr Otorhinolaryngol*. 135, 110112. doi:10.1016/j.ijporl.2020.110112.

Karns, C.M., Stevens, C., Dow, M.W., Schorr, E.M., Neville, H.J. (2017). Atypical white-matter microstructure in congenitally deaf adults: A region of interest and tractography study using diffusion-tensor imaging. *Hear Res*. 343, 72-82. doi:10.1016/j.heares.2016.07.008

Kittrell, A.P., Arjmand, E.M. (1997). The age of diagnosis of sensorineural hearing impairment in children. *Int J Pediatr Otorhinolaryngol*. 40(2-3), 97-106. doi:10.1016/s0165-5876(97)01506-1.

Kolb, B., Muhammad, A. (2014). Harnessing the power of neuroplasticity for intervention. *Front Hum Neurosci*. 8, 377. doi:10.3389/fnhum.2014.00377.

Kontorinis, G., Lloyd, S.K., Henderson, L., Jayewardene-Aston, D., Milward, K., Bruce, I.A., O'Driscoll, M., Green, K., Freeman, S.R. (2014). Cochlear implantation in children with auditory neuropathy spectrum disorders. *Cochlear Implants Int*. 15 Suppl 1, S51-54. doi:10.1179/1467010014z.000000000157.

Kothari, S., Keshree, N.K., Bhatnagar, S. (2015). Pediatric Cochlear Implantation-Why the Delay. *Indian J Otolaryngol Head Neck Surg*. 67(2), 165-169. doi:10.1007/s12070-015-0838-3

Kral, A., Dorman, M.F., Wilson, B.S. (2019). Neuronal Development of Hearing and Language: Cochlear Implants and Critical Periods. *Annu Rev Neurosci*. 42, 47-65. doi:10.1146/annurev-neuro-080317-061513.

Kral, A., Sharma, A. (2012). Developmental neuroplasticity after cochlear implantation. *Trends Neurosci*. 35(2), 111-122. doi:10.1016/j.tins.2011.09.004.

Kral, A., Yusuf, P.A., Land, R. (2017). Higher-order auditory areas in congenital deafness: Top-down interactions and corticocortical decoupling. *Hear Res*. 343, 50-63. doi:10.1016/j.heares.2016.08.017.

Kuchta, J. (2007). Twenty-five years of auditory brainstem implants: perspectives. *Acta Neurochir Suppl*. 97(Pt 2), 443-449. doi:10.1007/978-3-211-33081-4_51.

Kupers, R., Ptito, M. (2014). Compensatory plasticity and cross-modal reorganization following early visual deprivation. *Neurosci Biobehav Rev*. 41, 36-52. doi:10.1016/j.neubiorev.2013.08.001.

le Roux, T., Vinck, B., Butler, I., Cass, N., Louw, L., Nauta, L., Schlesinger, D., Soer, M., Tshifularo, M., Swanepoel de, W. (2016). Predictors of pediatric cochlear implantation outcomes in South Africa. *Int J Pediatr Otorhinolaryngol*. 84, 61-70. doi:10.1016/j.ijporl.2016.02.025.

Lieu, J.E.C., Kenna, M., Anne, S., Davidson, L. (2020). Hearing Loss in Children: A Review. *Jama*. 324(21), 2195-2205. doi:10.1001/jama.2020.17647.

Liu, Y., Dong, R., Li, Y., Xu, T., Li, Y., Chen, X., Gong, S. (2014). Effect of age at cochlear implantation on auditory and speech development of children with auditory neuropathy spectrum disorder. *Auris Nasus Larynx*. 41(6), 502-506. doi:10.1016/j.anl.2014.06.001.

Madden, C., Rutter, M., Hilbert, L., Greinwald, J.H., Jr., Choo, D.I. (2002). Clinical and audiological features in auditory neuropathy. *Arch Otolaryngol Head Neck Surg*. 128(9), 1026-1030. doi:10.1001/archotol.128.9.1026.

Manchaiah, V.K., Zhao, F., Danesh, A.A., Duprey, R. (2011). The genetic basis of auditory neuropathy spectrum disorder (ANSD). *Int J Pediatr Otorhinolaryngol*. 75(2), 151-158. doi:10.1016/j.ijporl.2010.11.023.

Mason, J.C., De Michele, A., Stevens, C., Ruth, R.A., Hashisaki, G.T. (2003). Cochlear implantation in patients with auditory neuropathy of varied etiologies. *Laryngoscope*. 113(1), 45-49. doi:10.1097/00005537-200301000-00009.

Merabet, L.B., Pascual-Leone, A. (2010). Neural reorganization following sensory loss: the opportunity of change. *Nat Rev Neurosci*. 11(1), 44-52. doi:10.1038/nrn2758.

Mittal, R., Ramesh, A.V., Panwar, S.S., Nilkanthan, A., Nair, S., Mehra, P.R. (2012). Auditory neuropathy spectrum disorder: its prevalence and audiological characteristics in an Indian tertiary care hospital. *Int J Pediatr Otorhinolaryngol*. 76(9), 1351-1354. doi:10.1016/j.ijporl.2012.06.005.

Myers, K., Nicholson, N. (2021). Cochlear Implant Behavioral Outcomes for Children With Auditory Neuropathy Spectrum Disorder: A Mini-Systematic Review. *Am J Audiol*. 30(3), 777-789. doi:10.1044/2021_aja-20-00175.

Niparko, J.K., Tobey, E.A., Thal, D.J., Eisenberg, L.S., Wang, N.Y., Quittner, A.L., Fink, N.E. (2010). Spoken language development in children following cochlear implantation. *Jama*. 303(15), 1498-1506. doi:10.1001/jama.2010.451.

Noblitt, B., Alfonso, K.P., Adkins, M., Bush, M.L. (2018). Barriers to Rehabilitation Care in Pediatric Cochlear Implant Recipients. *Otol Neurotol*. 39(5), e307-e313. doi:10.1097/mao.0000000000001777.

Omar, M., Qatanani, A., Kaleem, S.Z., McKinnon, B.J. (2022a). Sociodemographic Disparities in Pediatric Cochlear Implantation Access and Use: A Systematic Review. *Laryngoscope*. 132(3), 670-686. doi:10.1002/lary.29716.

Omar, M., Qatanani, A.M., Douglas, N.O., Nawash, B.S., Ibrahim, T., Kaleem, S.Z., McKinnon, B.J. (2022b). Sociodemographic disparities in pediatric cochlear implantation outcomes: A systematic review. *Am J Otolaryngol*. 43(5), 103608. doi:10.1016/j.amjoto.2022.103608.

Ozcebe, E., Sevinc, S., Belgin, E. (2005). The ages of suspicion, identification, amplification and intervention in children with hearing loss. *Int J Pediatr Otorhinolaryngol*. 69(8), 1081-1087. doi:10.1016/j.ijporl.2005.03.002.

Peng, K.A., Kuan, E.C., Hagan, S., Wilkinson, E.P., Miller, M.E. (2017). Cochlear Nerve Aplasia and Hypoplasia: Predictors of Cochlear Implant Success. *Otolaryngol Head Neck Surg*. 157(3), 392-400. doi:10.1177/0194599817718798.

Prendergast, S.G., Lartz, M.N., Fiedler, B.C. (2002). Ages of diagnosis, amplification, and early intervention of infants and young children with hearing loss: findings from parent interviews. *Am Ann Deaf*. 147(1), 24-30. doi:10.1353/aad.2012.0198.

Rajput, K., Saeed, M., Ahmed, J., Chung, M., Munro, C., Patel, S., Leal, C., Jiang, D., Nash, R. (2019). Findings from aetiological investigation of Auditory Neuropathy Spectrum Disorder in children referred to cochlear implant programs. *Int J Pediatr Otorhinolaryngol*. 116, 79-83. doi:10.1016/j.ijporl.2018.10.010.

Rance, G. (2005). Auditory neuropathy/dys-synchrony and its perceptual consequences. *Trends Amplif*. 9(1), 1-43. doi:10.1177/108471380500900102.

Rance, G., Barker, E.J. (2009). Speech and language outcomes in children with auditory neuropathy/dys-synchrony managed with either cochlear implants or hearing aids. *Int J Audiol*. 48(6), 313-320. doi:10.1080/14992020802665959.

Rance, G., Cone-Wesson, B., Wunderlich, J., Dowell, R. (2002). Speech perception and cortical event-related potentials in children with auditory neuropathy. *Ear Hear*. 23(3), 239-253. doi:10.1097/00003446-200206000-00008.

Rance, G., Starr, A., 2011. Auditory neuropathy/dys-synchrony, in: Seewald, R., Tharpe, A. (Eds.), Comprehensive handbook of pediatric audiology Plural Publishing, San Diego, pp. 225-242.

Rance, G., Starr, A. (2015). Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. *Brain*. 138(Pt 11), 3141-3158. doi:10.1093/brain/awv270.

Robertson, C.M., Howarth, T.M., Bork, D.L., Dinu, I.A. (2009). Permanent bilateral sensory and neural hearing loss of children after neonatal intensive care because of extreme prematurity: a thirty-year study. *Pediatrics*. 123(5), e797-807. doi:10.1542/peds.2008-2531.

Roush, P., Frymark, T., Venediktov, R., Wang, B. (2011). Audiologic management of auditory neuropathy spectrum disorder in children: a systematic review of the literature. *Am J Audiol*. 20(2), 159-170. doi:10.1044/1059-0889(2011/10-0032).

Ruben, R.J. (2018). Language development in the pediatric cochlear implant patient. *Laryngoscope Investig Otolaryngol*. 3(3), 209-213. doi:10.1002/lio2.156.

Saidia, A.R., Ruel, J., Bahloul, A., Chaix, B., Venail, F., Wang, J. (2023). Current Advances in Gene Therapies of Genetic Auditory Neuropathy Spectrum Disorder. *J Clin Med*. 12(3). doi:10.3390/jcm12030738

Santarelli, R., Rossi, R., Scimemi, P., Cama, E., Valentino, M.L., La Morgia, C., Caporali, L., Liguori, R., Magnavita, V., Monteleone, A., Biscaro, A., Arslan, E., Carelli, V. (2015). OPA1-related auditory neuropathy: site of lesion and outcome of cochlear implantation. *Brain*. 138(Pt 3), 563-576. doi:10.1093/brain/awu378.

Shallop, J. (2002). Auditory neuropathy/dys-synchrony in adults and children. *Sem Hear*(23), 215-223.

Sharma, A., Campbell, J. (2011). A sensitive period for cochlear implantation in deaf children. *J Matern Fetal Neonatal Med*. 24 Suppl 1(0 1), 151-153. doi:10.3109/14767058.2011.607614.

Sharma, A., Cardon, G., Henion, K., Roland, P. (2011). Cortical maturation and behavioral outcomes in children with auditory neuropathy spectrum disorder. *Int J Audiol*. 50(2), 98-106. doi:10.3109/14992027.2010.542492.

Shearer, A.E., Hansen, M.R. (2019). Auditory synaptopathy, auditory neuropathy, and cochlear implantation. *Laryngoscope Investig Otolaryngol*. 4(4), 429-440. doi:10.1002/lio2.288.

Shirvani, S., Jafari, Z., Motasaddi Zarandi, M., Jalaie, S., Mohagheghi, H., Tale, M.R. (2016). Emotional Perception of Music in Children With Bimodal Fitting and Unilateral Cochlear Implant. *Ann Otol Rhinol Laryngol*. 125(6), 470-477. doi:10.1177/0003489415619943.

Simon, M., Campbell, E., Genest, F., MacLean, M.W., Champoux, F., Lepore, F. (2020). The Impact of Early Deafness on Brain Plasticity: A Systematic Review of the White and Gray Matter Changes. *Front Neurosci*. 14, 206. doi:10.3389/fnins.2020.00206.

Starr, A., Rance, G., 2015. Auditory neuropathy. In: Celesia, G., Hickok, G. (Eds.), Handbook of Clinical Neurology. Elsevier, Edinburgh pp. 495-508.

Teagle, H.F., Roush, P.A., Woodard, J.S., Hatch, D.R., Zdanski, C.J., Buss, E., Buchman, C.A. (2010). Cochlear implantation in children with auditory neuropathy spectrum disorder. *Ear Hear*. 31(3), 325-335. doi:10.1097/AUD.0b013e3181ce693b.

Tomblin, J.B., Harrison, M., Ambrose, S.E., Walker, E.A., Oleson, J.J., Moeller, M.P. (2015). Language Outcomes in Young Children with Mild to Severe Hearing Loss. *Ear Hear*. 36 Suppl 1(0 1), 76s-91s. doi:10.1097/aud.0000000000000219.

Vesseur, A., Free, R., Snels, C., Dekker, F., Mylanus, E., Verbist, B., Frijns, J. (2018). Hearing Restoration in Cochlear Nerve Deficiency: the Choice Between Cochlear Implant or Auditory Brainstem Implant, a Meta-analysis. *Otol Neurotol*. 39(4), 428-437. doi:10.1097/mao.0000000000001727.

Walker, E., McCreery, R., Spratford, M., Roush, P. (2016). Children with Auditory Neuropathy Spectrum Disorder Fitted with Hearing Aids Applying the American Academy of Audiology Pediatric Amplification Guideline: Current Practice and Outcomes. *J Am Acad Audiol*. 27(3), 204-218. doi:10.3766/jaaa.15050.

Wolfe, J., 2020. Cochlear Implants: Audiologic Management and Considerations for Implantable Hearing Devices. Plural Publishing Inc., San Diego.

Yoshinaga-Itano, C. (1999). Benefits of early intervention for children with hearing loss. *Otolaryngol Clin North Am*. 32(6), 1089-1102. doi:10.1016/s0030-6665(05)70196-1.

Yoshinaga-Itano, C., Sedey, A.L., Coulter, D.K., Mehl, A.L. (1998). Language of early- and later-identified children with hearing loss. *Pediatrics*. 102(5), 1161-1171. doi:10.1542/peds.102.5.1161.

Zeng, F.G., Liu, S. (2006). Speech perception in individuals with auditory neuropathy. *J Speech Lang Hear Res*. 49(2), 367-380. doi:10.1044/1092-4388(2006/029).

Zhang, L., Links, A.R., Boss, E.F., White, A., Walsh, J. (2020). Identification of Potential Barriers to Timely Access to Pediatric Hearing Aids. *JAMA Otolaryngol Head Neck Surg*. 146(1), 13-19. doi:10.1001/jamaoto.2019.2877.

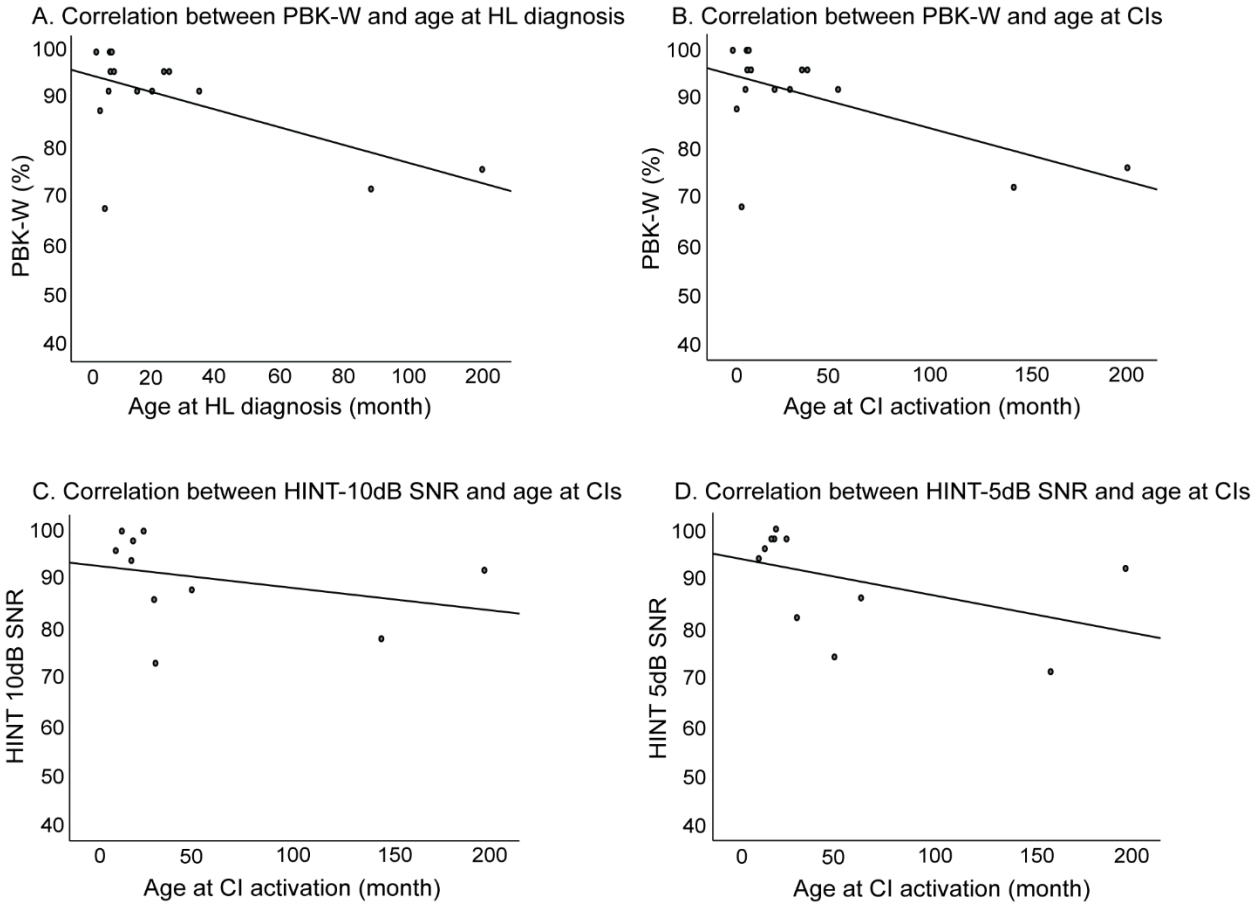

Figure 1. Correlation between age at HL diagnosis (A) and age at CI activation (B to D) with open-set speech perception test scores. CI: cochlear implant, HINT: Hearing In Noise Test in quiet and with two signal-to-noise ratios (SNR) of 10 and 5 dB, HL: hearing loss, and PBK-P: Phonetically Balanced Kindergarten test with phoneme stimuli.

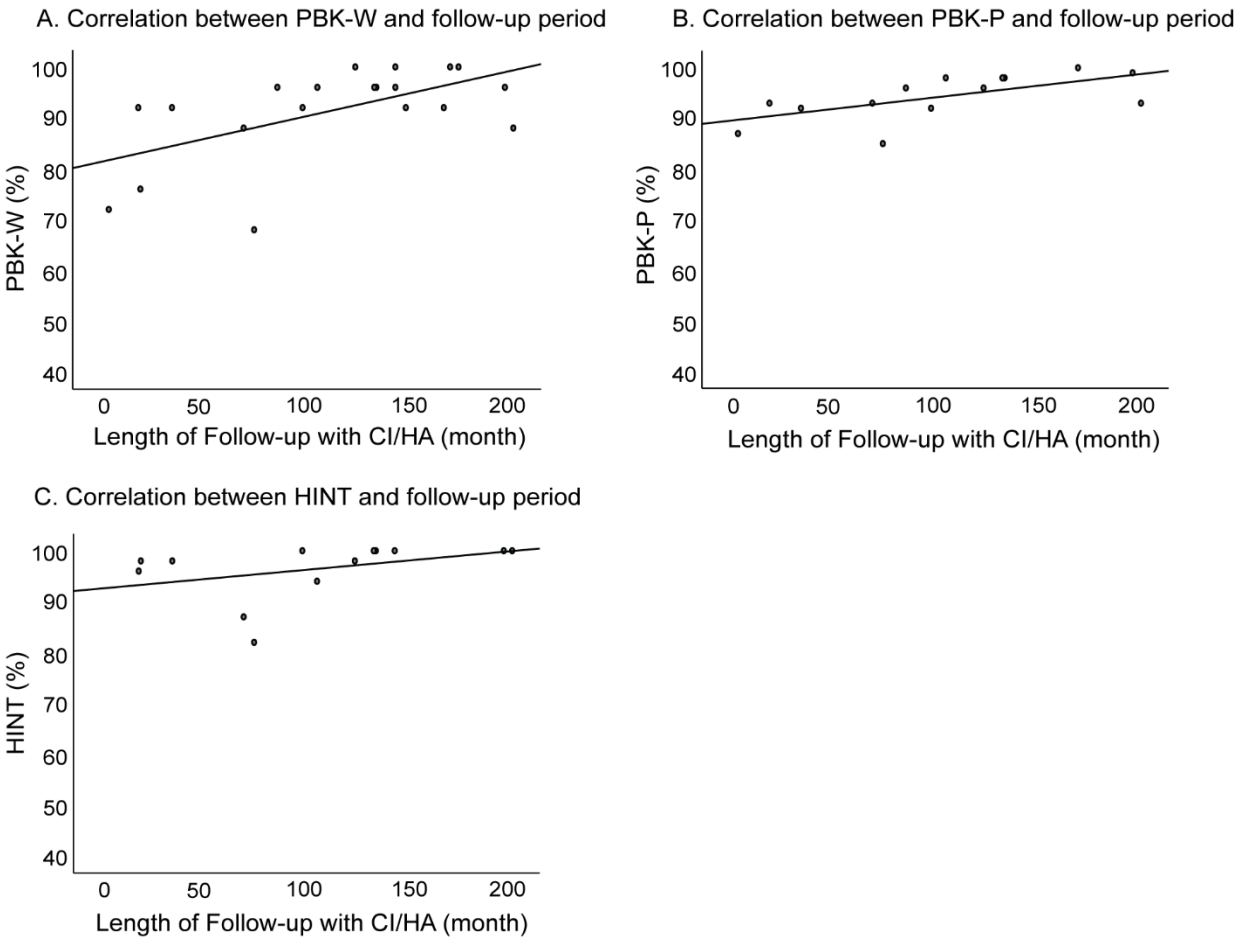

Figure 2. Correlation between the length of follow-up with CI/HA and open-set speech perception scores. CI: cochlear implant, HA: hearing aid, HINT: Hearing In Noise Test (in quiet), PBK: Phonetically Balanced Kindergarten test with both word (PBK-W) and phoneme (PBK-P) speech materials.

Table 1. Demographic characteristics of children with ANSD

ID	Sex	Device	CI/HA mode	Age at HL diagnosis (month)	Age at HAs (month)	Age at CIs (month)	Follow-up period (month)	Degree of HL	ADs/MCs	PB	NICU admission
CI1	F	Nucleus CI632	Bimodal	87.69	90.48	149.36	6	S-P		•	•
CI2	F	Nucleus CI532	Uni-R	4.80	13.15	31.30	20	P	•	•	•
CI3	F	Nucleus CI532	Bi	23.63	NR	24.63	31	P			
CI4	F	AB HiRes 90K	Uni-L	20.21	22.08	29.93	NR	S-P	•		•
CI15	F	AB HiRes 90K	Bi	5.29	12.62	17.94	172	S-P		•	
CI16	F	AB HiRes 90K	Uni-R	6.51	NR	62.46	133	P	•		
CI17	F	NF CI24RE	Bi	1.00	7.62	11.70	123	P			
CI8	F	AB HiRes Ultra CI HiFocus	Bi	7.85	NR	16.16	198	P		•	•
CI9	F	AB HiRes 90K	Uni-R	18.00	36.00	155.10	49	S-P			
CI10	F	AB HiRes 90K	Bi	122.76	123.47	142.88	21	Mo-S	•		
CI11	F	AB HiRes Ultra CI HiFocus	Bi	12.12	13.50	30.03	182	NR			
CI12	M	Nucleus CI532	Bimodal	18.63	20.24	193.80	20	S-P	•	•	•
CI13	M	Nucleus CI512	Bi	NR	NR	43.99	36	NR	•	•	•
CI14	M	MedEl Mi1000 Concerto	Uni-R	3.71	5.55	30.62	75	S-P	•		
CI15	M	AB HiRes 90K	Bi	4.50	NR	11.04	82	P			

CI16	M	NF CI24RE	Uni-R	2.20	16.62	31.30	70	P	•	•	•
CI17	M	AB HiRes 90K	Uni-L	143.64	144.95	156.58	56	Mo	•	•	
CI18	M	AB HiRes 90K	Bi	5.45	14.19	27.20	142	S-P	•	•	•
CI19	M	Nucleus CI512	Uni-L	4.60	10.38	57.69	133	S-P		•	•
CI20	M	Nucleus CI512	Bi	33.48	34.00	52.70	147	S-P	•		
CI21	M	AB HiRes 90K	Bi	13.90	14.85	19.38	165	S-P	•	•	•
CI22	M	NF CI24RE	Bi	29.21	34.27	55.69	159	S-P	•		•
CI23	M	NFCI24RE	Bi	22.34	23.16	25.46	132	P			
CI24	M	AB HiRes 90K	Uni-R	13.73	14.65	17.97	NR	NR	•		
CI25	M	AB HiRes 90K	Uni-R	5.49	7.89	49.25	105	S-P	•		
CI26	M	AB HiRes 90K	Bi	6.60	10.02	14.69	194	S-P	•	•	•
CI27	M	AB HiRes 90K	Bi	1.00	11.66	20.24	142	NR	•	•	
HA1	F	Phonak Sky M90-SP	Uni-L	5.91	14.39	149.36	168	R: Mi-S L: Mi-P			
HA2	F	Phonak Sky V70P	Bi	5.55	7.33	NA	121	Mo-S	•		
HA3	F	Phonak Sky B50P	NR	2.83	11.66	NA	44	Mi-S	•	•	•
HA4	M	Oticon Safari 600 P	Uni-R	3.06	3.98	NA	132	S	•		
HA5	M	Oticon Safari 600 P	Bi	8.15	26.87	NA	91	Mo-S	•	•	
HA6	M	NR	Uni-l	24.00	25.00	NA	86	R: N L: P			

HA7	M	Phonak Sky Q50-SP	Bi	49.22	52.37	NA	124	Mi-S	•		
JA8	M	Phonak iLink S 311 Forte NB	Bi	7.52	17.87	NA	66	Mi-S			
HA9	M	Phonak Naida S V SP	NR	22.54	24.15	NA	27	R: Mi-P L: Mi-S			
HA10	M	Phonak Sky M50-PR	Uni-L	4.90	49.71	NA	98	R: Mi L: Mi-Mo	•	•	•
HA11	M	Oticon Opn S2	Bi	1.54	91.60	NA	6	R: N L: P			

Bi: bilateral, CI: cochlear implant, F: female, HA: hearing aid, L: left ear, m: male, Mi: mild, Mo: moderate, NA: not applicable, NF: Nucleus Freedom, NR: not reported, P: profound, R: right ear, S: severe, Uni: unilateral.

Table 2. Age at HL diagnosis, HA fitting, and CI activation based on the onset of HL

Onset of HL	**Age at HL Diagnosis (months) (N = 38)**					**Age at HAs (months) (N = 38)**					**Age at CIs (months) (N = 27)**				
	n	Mean	SD	Median	Range	n	Mean	SD	Median	Range	n	Mean	SD	Median	Range
Congenital or early-onset	23	5.68	4.07	5.29	1.0-20.21	20	18.43	19.85	12.88	3.98-91.60	15	29.43	15.94	29.93	11.04-62.46
Late-onset	9	39.11	40.65	24.00	13.73-143.64	9	40.82	40.72	25.00	14.65-144.95	6	54.63	52.60	39.08	17.97-156.58
Unknown	5	54.14	48.38	23.63	18.00-122.76	4	67.54	47.91	63.24	20.24-123.47	6	118.29	67.70	146.12	24.63-193.80

CI: cochlear implant, HA: hearing aid, HL: hearing loss, SD: standard deviation.

Table 3. Mean age at HL diagnosis, HA fitting, and CI activation in children with a history of NICU, preterm birth, or ADs/MCs

Risk factors	Age at HL Diagnosis (months)						Age at HAs (months)						Age at CIs (months)					
	Yes			No			Yes			No			Yes			No		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
NICU (n= 15/38)	10.84	7.22	8.52	26.16	7.52	39.17	20.63	16.62	11.29	36.90	16.26	41.92	47.37	31.30	50.67	59.87	30.32	56.24
PB (n= 18/38)	20.44	6.60	37.60	20.29	12.92	27.25	30.58	15.73	36.73	30.40	22.08	32.36	59.97	31.30	62.69	49.96	30.32	44.98
ADs/MCs (n= 17/27)	22.95	6.55	37.77	16.56	7.85	21.39	30.45	14.85	37.12	30.56	20.51	29.29	57.64	31.30	53.61	49.91	25.04	55.55

ADs/MCs: additional disabilities/medical comorbidities, HA: hearing aid, HL: hearing loss, NICU: neonatal intensive care unit, PB: preterm birth, SD: standard deviation.

Table 4. Scores for five open-set speech perception tests

Speech perception test scores	N	Mean	Median	SD	Range
PBK-W	20	91.40	94.00	9.20	68.00-100
PBK-P	14	94.28	94.50	4.44	85.00-100
HINT-quiet	13	96.38	98.00	5.67	82.00-100
HINT-10dB SNR	13	90.91	93.00	8.43	73.00-100
HINT-5dB SNR	13	87.53	92.00	11.02	71.00-100

HINT: hearing in noise test in quiet and with two signal-to-noise ratios (SNR) of 10dB and 5dB, PBK: Phonetically Balanced Kindergarten test with word (PBK-W) and phoneme (PBK-P) speech materials, SD: standard deviation.

Table 5. Results of a Forward Linear multiple Regression Model to identify variables contributing to speech perception outcomes

Speech perception test scores	**Predictor**	**Regression coefficient**	**F**	**p**	**Standardized coefficient Beta**	**p**
PBK-W	Follow-up period	0.448	11.562	0.005	0.700	0.014
PBK-P	Follow-up period	0.525	6.625	0.042	0.724	0.034
HINT in quiet	Bilateral amplification	0.605	10.723	0.014	0.778	0.024
HINT – 10dB SNR	Bilateral amplification	0.418	7.455	0.026	0.695	0.012
HINT – 5dB SNR	Bilateral amplification	0.772	20.750	0.002	0.850	0.002

CI: cochlear implant, HINT: Hearing in Noise Test in quiet and with two signal-to-noise ratios (SNR) of 10dB and 5dB, PBK: Phonetically Balanced Kindergarten test with word (PBK-W) and phoneme (PBK-P) speech materials.

Table 6. Mean age at HL diagnosis, HA fitting, and CI activation in previous studies on children with SNHL or ANSD

Study	Country	Study design	Sample size	ADs/MCs (%)	Degree/type of HL	Age at HL diagnosis (months)	Age at HAs (months)	Age at CIs (months)
Present Study	Canada	Retrospective	23	60.80%	Mild to profound/ANSD	5.68 (4.04)[a]	18.43 (19.85)	29.43 (15.94)
le Roux et al. 2016	South Africa	Retrospective	122	Yes, % NR	Severe to profound/SNHL	16.10 (10.00)	NA	45.60 (32.50)
Kontorinis et al. 2014	UK	Retrospective	27	30%	Profound/ ANSD	NA	NA	35.40 (19-68)
Budenz et al. 2013	USA	Retrospective	17	No	Profound/ANSD	NA	NA	34.06 (17.53)
			17	No	Profound/SNHL	NA	NA	32.35 (18.08)
Ching et al. 2013a	Australia	Prospective	47	30%	Mild to severe/ANSD	3.30 (2.20)	6.20 (3.50)	18.20 (6.60)
Ching et al. 2013b	Australia	Prospective	451	24%	Mild to profound	6.00 (8.20)	8.90 (8.80)	17.70 (9.00)
Fitzpatrick et al. 2011	Canada	Retrospective	43	9.30%	Profound/SNHL (2 with ANSD)	9.0 (5.10-15.80)	11.30 (6.60-17.40)	22.30 (15.10-34.70)
Jafari et al. 2007	Iran	Retrospective	86	47.7%	Severe to profound/SNHL	15.20 (16.80)	20.50 (11.10)	NA
Ozcebe et al. 2005	Turkey		199	Yes, % NR	Severe to profound/SNHL	19.40 (11.60)	26.50 (14.80)	NA
Prendergast et al. 2002	USA	Prospective	72	Yes, % NR	Severe to profound/SNHL	14.58 11.13)	19.05 (11.57)	NA

Kitteral and Arjmand, 1997	USA	Retrospective	291	30%	Severe to profound/SNHL	20.20	31.70	NA
Harrison and Roush, 1996	USA	Prospective	331	No, (n=42)	Mild to moderate/SNHL	22.00 (15.00)	28.00 (13.00)	NA
				No, (n=118)	Severe to profound/SNHL	13.00 (10.00)	16.00 (13.00)	NA
				Yes, (n=39)	Mild to moderate/SNHL	12.00 (27.00)	22.00 (28.00)	NA
				Yes, (n=132)	Severe to profound/SNHL	12.00 (14.00)	15.00 (13.00)	NA

[a] Values in parenthesis show the standard deviation (SD) or range.

ADs/MCs: additional disabilities and/or medical comorbidities, ANSD: auditory neuropathy spectrum disorder, CI: cochlear implant, HA: hearing aid, HL: hearing loss, NA: not applicable, NR: not reported, SNHL: sensorineural hearing loss.

Chapter 3

Title:

Prognostic Value of Electrophysiologic and MRI Findings for Cochlear Implant Outcomes in Children: A Systematic Review

Short Title:

Electrophysiologic and Imaging Predictors of Pediatric Cochlear Implantation Outcomes

Authors: Zahra Jafari[1], Elizabeth M. Fitzpatrick[1,2], David R. Schramm[3,4], Isabelle Rouillon[5], Amineh Koravand[1]

[1]Audiology and Speech-Language Pathology Program, University of Ottawa, Ottawa, Ontario, Canada.

[2]Child Hearing Laboratory, CHEO Research Institute Ottawa, Ontario, Canada.

[3]Department of Otolaryngology-Head and Neck Surgery, University of Ottawa, Ottawa, Ontario, Canada.

[4]Department of Otolaryngology-Head and Neck Surgery, The Ottawa Hospital, Ottawa, Ontario, Canada.

[5]Department of Pediatric Otolaryngology, AP-HP, Hôpital Necker-Enfants Malades, Paris, France.

Corresponding author: Amineh Koravand

Jafari Z, Fitzpatrick EM, Schramm DR, Rouillon I, Koravand A. Prognostic Value of Electrophysiologic and MRI Findings for Cochlear Implant Outcomes in Children: A Systematic *Submitted*. Under review.

Abstract

Purpose: MRI, electric compound action potentials (eCAP), and electric auditory brainstem responses (eABR) are among the routine assessments performed before and/or after cochlear implantation (CI). The objective of this review was to systematically summarize and critically appraise existing evidence of the prognostic value of eCAP, eABR, and MRI for predicting post-CI speech perception outcomes in children.

Method: The present systematic review (SR) was guided by the PRISMA 2020 statement. Three electronic databases (ProQuest, PubMed, and Scopus) were searched with no restrictions on language, publication status, or year of publication. Studies on children identified with sensorineural hearing loss (SNHL), auditory neuropathy spectrum disorders (ANSD), cochlear nerve deficiency (CND), or cochleovestibular nerve (CVN) abnormalities reporting the relevance of eCAP, eABR, and/or MRI results to CI outcomes were included. Methodological quality and strength of evidence were assessed by the Crowe Critical Appraisal Tool (CCAT) and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool, respectively.

Results: Of the 25 included studies, the relevance of eCAP, eABR, and/or MRI findings to CI outcomes was reported in 10, 11, and 11 studies, respectively. The studies were strongly in support of the prognostic value of eABR and MRI for post-CI outcomes. However, the relevance of eCAP findings to speech perception outcomes was uncertain.

Conclusions: Despite promising findings, these should be interpreted with caution given the observational, retrospective design of the included studies, the heterogeneity of the population, and limited control of confounding factors in the included studies.

Keywords: Electric compound action potentials; Electric auditory brainstem responses; MRI; Auditory neuropathy spectrum disorder; Cochlear nerve deficiency; Cochlear implant; Speech perception; Predictor

Introduction

Cochlear implants (CI) are one of the most successful neuroprosthetic devices in neurorehabilitation (Kuchta, 2007; Lim et al., 2009). Compared to other sensory implants, the advantage of a CI results from the fact that the perception of auditory information is largely based on temporal processing that can be effectively transmitted by only a few electrodes. In contrast, the function of other sensory systems, especially the visual system, is based on the processing of multiple components (e.g., the object's form, texture, motion, depth, color, and luminance) (Kandel et al., 2021), implicating more individual channels to transmit information. The output of this complex signal processing, however, might not provide the expected resolution (Kuchta, 2007). In addition, the auditory nerve fibers are better stimulated or synchronized with electric stimulation relative to acoustic stimulation (Chaudhry et al., 2020). The CI bypasses the cochlear and synaptic parts of the auditory system, which might be involved with inner ear abnormalities or auditory neuropathy spectrum disorder (ANSD), and directly stimulates the spiral ganglion neurons, leading to the transmission of electrical signals to the midbrain (Shearer and Hansen, 2019). Compared to acoustic stimulation, direct nerve stimulation enhances neural synchrony, which allows the development of fundamental speech and hearing skills (Chaudhry et al., 2020). Further, CI technology entails various fitting strategies that allow simplifying the early device programming proportionate to years of auditory deprivation or the needs of children with additional disabilities. In the long term, the fitting program can be modified according to periodic assessments of CI outcomes (Wilson, 2011; Wilson et al., 2011).

The CI is currently the intervention option of choice for most children with severe to profound sensorineural hearing loss (SNHL), especially those who show poor progress with

properly fitted hearing aids (HAs) (JCIH, 2019). ANSD is an auditory disorder that is characterized by the involvement of the peripheral auditory system leading to impaired temporal coding of acoustic signals and impaired auditory perception (Santarelli et al., 2021). It has a heterogeneous clinical profile, encompassing various acquired, genetic, and congenital aetiologies (Chaudhry et al., 2020; Hall, 2015; Rance and Starr, 2015). Children with ANSD frequently show poor progress with HAs (Breneman et al., 2012). Based on the anatomic locus of dysfunction and audiologic and electrophysiologic findings, ANSD is broadly classified into "presynaptic and postsynaptic disorders". In presynaptic ANSD (or auditory synaptopathy, auditory dyssynchrony) such as otoferlin and DIAPH 3 mutations, the lesion site is the inner hair cells or ribbon synapses. In postsynaptic ANSD (e.g., due to OPA1 gene mutation in syndromic dominant optic atrophy [DOA+], or PM22 and MPZ gene mutations in Charcot-Marie-Tooth disease type A [CMT 1A] and type B [CMT 1B], respectively) (Chaudhry et al., 2020), dysfunction can occur at multiple sites along the auditory nerve pathway, including unmyelinated auditory nerve dendrites or auditory ganglion cells and their myelinated axons and dendrites (Hall, 2015; Rance and Starr, 2015).

Like children with SNHL, better outcomes for ANSD are associated with receiving CIs before three years of age (Ching et al., 2013a; Ching et al., 2013b; Niparko et al., 2010). Although most children with SNHL can achieve typical rates of speech, language, and academic development with CIs (Leigh et al., 2011), the post-CI speech perception performance of children with ANSD is highly variable (Bo et al., 2022; Cupples et al., 2018; Myers and Nicholson, 2021; Peng et al., 2017; Rajput et al., 2019; Rance and Starr, 2015; Vesseur et al., 2018). Although the majority of children with ANSD can achieve speech understanding, language development, and communication outcomes equivalent to their peers with SNHL (Madden et al., 2002; Mason et al.,

2003; Rance and Barker, 2009; Santarelli et al., 2015; Shallop, 2002; Teagle et al., 2010; Zeng and Liu, 2006), a subgroup of children with cochlear nerve deficiency (CND) may attain minimal benefit from CIs and fail to develop functionally useful auditory communication skills (Gibson and Sanli, 2007; Roush et al., 2011; Teagle et al., 2010). CND was initially described in 1997 (Casselman et al., 1997). It is characterized by a very abnormal auditory nerve structure, including a small (hypoplastic) or absent (aplastic) cochlear nerve, which is identified with a high-resolution MRI (Hall, 2015; Roche et al., 2010). In addition, almost one-third of children with ANSD have at least one additional disability other than hearing loss (Ching et al., 2013a).

In ANSD, among various contributing factors to heterogeneity in patients and inconsistency in the literature (e.g., the lesion site, comorbid symptoms, additional disabilities, age at CI activation, duration of CI use, cognitive function, socioeconomic status, sex, and maternal education) (Bo et al., 2022; Cupples et al., 2018; Myers and Nicholson, 2021; Peng et al., 2017; Rajput et al., 2019; Rance and Starr, 2015; Vesseur et al., 2018), the lesion site plays a prominent role (Bo et al., 2022; Ching et al., 2013a; Hall, 2015; Myers and Nicholson, 2021; Starr and Rance, 2015). For this reason, high-resolution MRI is considered the gold standard in identifying postsynaptic ANSD and evidence of CND. In addition, both intraoperative and postoperative electric compound action potential (eCAP) and electrically evoked auditory brainstem response (eABR) are commonly used to determine the excitability of the cochlear nerve (CN) and may have predictive value for functional outcomes of electric amplification (Nada et al., 2022). While some existing findings support the prognostic value of MRI (Jeong and Kim, 2013a; Kari et al., 2022) and intraoperative and/or postoperative electrophysiologic results (Dutt et al., 2021; Gibson et al., 2009; Yamazaki et al., 2015) for CI outcomes, other studies do not support this application (Chao

et al., 2016; Nikolopoulos et al., 2000). The objective of this review was to systematically summarize and critically appraise existing evidence on the prognostic value of early auditory electrophysiologic measures (i.e., intraoperative and/or postoperative eCAP and eABR) and MRI findings for post-CI speech perception performance in children diagnosed with ANSD, cochleovestibular nerve (CVN) abnormalities, or SNHL. We hypothesized that combined electrophysiologic and MRI findings would have predictive value for CI outcomes.

Method

Search Strategy

The comprehensive literature search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021) (Appendix IV). Three electronic databases were searched from their inception dates to July 2023: ProQuest, PubMed, and Scopus. The following combined search terms were used to identify relevant evidence: 1) “neural response telemetry” OR “neural response imaging”, OR “auditory nerve response telemetry” AND “cochlear implant” AND “speech perception”, 2) “electric compound action potential” AND “cochlear implant” AND “speech perception”, 3) “electric auditory brainstem response” AND “cochlear implant” AND “speech perception”, and 4) “MRI” AND “cochlear implant” AND “speech perception”. References to included studies were manually checked for missing articles in the database search. Both published reviews and preprints were examined if applicable. The search had no restrictions on language, publication status, or year of publication. The SR protocol was established before the conduct of the review and uploaded to the PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO, registration number: CRD42023408883).

Inclusion and Exclusion Criteria

The criteria for inclusion in the systematic review were defined in terms of participants, interventions, comparators, outcomes, and study designs (PICOS) (Morgan et al., 2018) as follows: (P) studies on children identified with SNHL, ANSD, and/or CVN abnormalities who were using one or two CIs, (I) tests of intraoperative or postoperative eCAP (including studies reporting neural response telemetry [NRT], auditory nerve response telemetry [ANRT] or neural response imaging [NRI]), and/or eABR, and/or pre-implantation MRI; (C) peers with SNHL with CIs or no control group; (O) speech perception performance based on the results of standard speech and/or language tests and/or standard, relevant questionnaires; and (S) randomized controlled trials (RCTs), or cross-sectional, case-control, retrospective, or prospective studies with or without a control group. Reviews, books, case reports, and editorials were excluded.

Literature Screening and Data Extraction

Duplicates were eliminated using Endnote software (Thomson Reuters, Philadelphia, Pennsylvania, USA, version X7). The final papers were selected through a three-stage process: title screening, abstract screening, and full-text screening. Papers that did not meet the inclusion criteria were excluded from each section. In the case of uncertainty, first, the abstracts and then the full texts were screened. The three stages were independently reviewed by two reviewers (ZJ and AK). Overall, there was complete agreement between the reviewers on the included papers.

Quality Assessment

The Crowe Critical Appraisal Tool (CCAT) was used for quality measurement (Crowe et al., 2012) (Appendix V). The CCAT is one of the few instruments that has undergone both reliability and validity evaluations and applies to appraising different research designs (Crowe and

Sheppard, 2011; Crowe et al., 2012). In each paper, eight aspects including preliminaries, introduction, design, sampling, data collection, ethical issues, results/findings, and discussion are evaluated using a 6-point rating scale (from zero to five for each category), and the total score is 40 (Jafari et al., 2021).

Assessing the Certainty of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (Guyatt et al., 2008) was used to rate the quality of evidence for each outcome. The quality of evidence reflects the extent to which we are confident that an estimate of the effect is correct. Using GRADE, the quality of evidence is rated for each outcome across studies or for a body of evidence, not for every study as a single unit (Schünemann et al., 2013). A set of five domains constructs the GRADE approach to rate the quality of evidence including 1) studies' methodological limitations (the judgment that the findings of included studies for a given outcome are adequately protected against bias based on the design and conduct of the studies), 2) indirectness of evidence (how closely available evidence measures an outcome of interest), 3) imprecision (when studies include relatively few patients and few events and have a wide confidence interval [CI] or standard deviation [SD] around the estimate of the effect), 4) inconsistency (the degree of similarity in the direction and/or magnitude of effects across individual studies), and 5) publication bias (when authors, journals, or both decide to publish or report research findings based on their direction or magnitude of effect). Although the quality of evidence represents a continuum, the GRADE approach results in one of four grades: high (high confidence that the true effect lies close to the effect estimate), moderate (moderate confidence in the effect estimate), low (limited confidence in the effect estimate), or very low (very little confidence in the effect estimate) (Schünemann et al., 2013). For this SR, we used the GRADE

approach recommended to assess the certainty in evidence when a meta-analysis could not be performed and data are summarized narratively (Murad et al., 2017). The certainty in evidence was assessed by one main researcher (ZJ) and then verified by another (AK).

Results

Systematic Review

The database search yielded 1,887 papers, including 1,027 duplicate records that were removed (Figure 1). After screening titles, 816 more records were eliminated including out-of-scope papers (n = 480), reviews (n = 145), abstracts (n = 91), posters (n = 16), case reports (n = 35), editorials (n = 5), and books (n = 44). Out-of-scope papers refer to publications that did not meet the inclusion criteria (i.e., PICOS). This initial screening resulted in a set of 44 papers. Subsequently, 18 more papers were eliminated during the screening of abstracts, consisting of out-of-scope publications = 15, reviews = 1, and case reports = 2. Of the 26 studies remaining for full-text review, 1 paper was removed because of evidence of duplicate publication (i.e., the paper that was removed (Kim et al., 2011) was part of a larger study published later (Jeong and Kim, 2013b)), leaving 25 studies appropriate for narrative analysis (Tables 1, 2, and 3). The reference lists for the selected publications were also hand-searched for any additional related publications. No further related articles, however, were found.

Characteristics of the Included Studies

Tables 1, 2, and 3 summarize the characteristics of articles included in the systematic review, consisting of the first author and year of publication, country of origin, participants (the total number, age, and sex, per subgroup if applicable), age at CIs (month), type of CI device, use of one or two CIs (unilateral or bilateral), follow-up period (date of outcome measures from CI

activation per month), electrophysiologic results (intraoperative and/or postoperative eCAP and/or eABR), MRI results, and summary of primary findings.

eCAP Measures: Table 1 provides a summary of studies reporting the prognostic value of eCAP for CI outcomes. Of the 10 included studies (eight retrospective (Buchman et al., 2011; Cosetti et al., 2010; Fulmer et al., 2011; Guedes et al., 2007; Jeong and Kim, 2013a; Song et al., 2010; Teagle et al., 2010; Valero et al., 2012) and two prospective (Attias et al., 2017; Motasaddi Zarandy et al., 2018)), four were on children with ANSD (Attias et al., 2017; Fulmer et al., 2011; Jeong and Kim, 2013a; Teagle et al., 2010), three on children with CND (Buchman et al., 2011; Song et al., 2010; Valero et al., 2012), two on children with SNHL (Cosetti et al., 2010; Motasaddi Zarandy et al., 2018), and one did not report the etiology of hearing disorder for the study population (Guedes et al., 2007). Two of the studies on children with ANSD had a matched control group with SNHL (Attias et al., 2017; Valero et al., 2012). The sample size of the included studies ranged from 10 (Fulmer et al., 2011; Motasaddi Zarandy et al., 2018) to 97 (Cosetti et al., 2010), and the follow-up time was between 6 (Motasaddi Zarandy et al., 2018) to 72.08 (Jeong and Kim, 2013a) months. Of the 10 included studies, intraoperative and/or postoperative eCAP tests were reported in four (Buchman et al., 2011; Cosetti et al., 2010; Guedes et al., 2007; Teagle et al., 2010) and six (Attias et al., 2017; Buchman et al., 2011; Fulmer et al., 2011; Jeong and Kim, 2013a; Motasaddi Zarandy et al., 2018; Song et al., 2010; Valero et al., 2012) studies, respectively. To evaluate the CI outcomes, studies used a wide range of standard behavioral assessments and/or questionnaires including the Mono-syllabic Word Test (MWT), Categories of Auditory Performance (CAP) test, Speech Intelligibility Rating (SIR) test, Bamford-Kowal-Bench (BKB) sentence test, Phonetically Balanced Kindergarten (PBK) test, early speech perception (ESP) test, Word Intelligibility by Picture Identification (WIPI) test, Glendonald Auditory Screening Procedure (GASP) test,

consonant identification test, Consonant-Nucleus-Consonant (CNC) test, lexical neighborhood test (LNT), Multi-syllable Lexical Neighborhood Test (MLNT), Newsha developmental scale, and Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS).

eABR Measures: Table 2 summarizes the main characteristics of 11 studies, one prospective (Nikolopoulos et al., 2000) and 10 retrospective (Gibson et al., 2009; Jeon et al., 2013; Jeong and Kim, 2013a; Jin et al., 2013; Kim et al., 2008; Motasaddi Zarandy et al., 2018; Song et al., 2010; Valero et al., 2012; Walton et al., 2008; Yamazaki et al., 2015), reporting the prognostic value of eABR for CI outcomes. Of the 11 included studies, three were on children with SNHL (Gibson et al., 2009; Nikolopoulos et al., 2000; Walton et al., 2008), four on children with ANSD (Jeon et al., 2013; Jeong and Kim, 2013a; Valero et al., 2012; Walton et al., 2008), two on children with CND (Jin et al., 2013; Yamazaki et al., 2015), and one on children with CVN abnormalities (Kim et al., 2008). The sample size of the included studies varied between 11 (Jeon et al., 2013) and 245 (Gibson et al., 2009). Studies varied widely in the follow-up period (i.e., equal to or more than six months). In the majority of the included studies, the follow-up time was equal to or greater than 12 months. eABR was recorded intraoperatively (Gibson et al., 2009; Jin et al., 2013; Nikolopoulos et al., 2000; Wang et al., 2015; Yamazaki et al., 2015) or postoperatively (Jeon et al., 2013; Jeong and Kim, 2013a; Kim et al., 2008; Valero et al., 2012; Walton et al., 2008) in an equal number of studies (n = 5). The studies used a variety of standard behavioral assessments and/or questionnaires as outcome measures consisting of MWT, open-set and closed-set speech tests, the logatome test (64 vowel-consonant-vowel [VCV] words), ESP, GASP for word and sentence tests, WIPI, CAP, SIR, BKB phoneme and word tests, long and short vowel recognition tests, LNT phoneme test, Melbourne speech perception score (MSPS) test, minimal pair test, Iowa sentence test,

Northwestern University children's perception of speech (NUCHIP) test, Connected Discourse Tracking (CDT) test, MLNT, LNT, and IT-MAIS.

MRI Findings: Table 3 provides a summary of 11 retrospective articles on children with CND (Birman et al., 2016; Chao et al., 2016; Chung et al., 2018; Han et al., 2019; Jeong and Kim, 2013a; Teagle et al., 2010; Valero et al., 2012; Yamazaki et al., 2015) or CVN abnormalities (Gaurav and Rajguru, 2019; Jeong and Kim, 2015; Kari et al., 2022) reporting on the prognostic value of MRI measures for CI outcomes. The number of participants varied between 10 (Chao et al., 2016) and 59 (Jeong and Kim, 2015) across the studies. Among the included studies, only one study on children with CND had a control group with SNHL (Chao et al., 2016). To assess CI outcomes, studies used various standard behavioral tests and/or questionnaires including speech awareness thresholds (SAT), open-set MWT, picture vocabulary test, ESP, WIPI, GASP, CNC word test, Hearing in Noise Test (HINT), AZBio sentence lists, CAP, BKB phoneme and word tests, LNT, MLNT, MAIS, and IT-MAIS.

Given the high level of heterogeneity of the included studies, especially in terms of the characteristics of the study populations, age at CIs, follow-up periods, and outcome measures, a meta-analysis was not conducted, and the findings were narratively discussed.

Methodological Quality of Evidence

The included studies were assessed for methodological quality using CCAT (Crowe et al., 2012). Table 4 summarizes each study's total score as well as the scores for each of the eight components of CCAT. The methodological quality of the included studies varied between 50.0 and 82.5% (mean: 68.50%). The CCAT total score was equal to or higher than 70% in 12 studies. The studies were deficient in several aspects, particularly study design (e.g., not reporting potential sources of selection bias and confounding variables), sampling (i.e., not reporting the sampling

method, suitability of the sampling method, the method of sample size calculation, the suitability of sample size, and/or inclusion and exclusion criteria), data collection (i.e., not reporting incomplete or lost data and how their impacts were taken into account), ethical considerations (i.e., not reporting informed consent, ethical approval, funding, and/or conflicts of interest), data presentation (i.e., not reporting demographic and other characteristics of participants, suitability of statistical analyses and interpretation of findings, and potential statistical adjustments applied to consider the impact of confounding factors), and discussion (i.e., not addressing potential bias or confounding, study limitations, and/or suggestions for future research).

Certainty of Evidence

The GRADE tool was used to narratively synthesize the certainty in the evidence for each of the three primary outcomes (Table 5). For the first outcome, the prognostic value of eCAP for CI outcomes, evidence was rated with "low certainty" in the domains of methodological limitations, imprecision, and inconsistency, and with "high certainty" in the domains of indirectness and publication bias. For two other outcomes, the prognostic value of eABR and MRI for CI outcomes, evidence was rated with "low certainty" for methodological limitations and imprecision, and with "high certainty" for inconsistency, indirectness, and publication bias.

Discussion

In this systematic review, studies on the prognostic value of intraoperative and/or postoperative eCAP and/or eABR, and preoperative MRI for post-CI speech perception outcomes were reviewed. Although current evidence was not firmly in support of the predictive value of eCAP, the eABR findings (e.g., eV latency, eV threshold, or eABR morphology/presence) were predominantly predictors of post-CI outcomes. Similarly, in MRI studies, irrespective of the lesion site (SNHL, ANSD, CND, or CVN abnormalities), the MRI findings (e.g., internal auditory canal

[IAC] midpoint diameter, number of auditory nerve fibers in IAC, cochlear nerve canal [CNC] diameter, and/or the area ratio of cochlear nerve [CN] to facial nerve [FN]) were predictors of post-CI speech perception performance. In the following paragraphs, the findings for each measurement tool are discussed taking into account the methodological quality and certainty of the evidence.

Prognostic Value of eCAP Findings to CI Outcomes

ECAP is an electrophysiologic test that measures the auditory nerve response to electrical stimulation after the insertion of CI electrodes, and it is similar to the first wave of ABR. NRT is a technique used to measure eCAP intraoperatively or postoperatively. In children with SNHL, NRT results within normal limits are an indication of the proper placement and function of electrodes and the potential success of the implant. Although eCAP recording is an integral part of initial device activation and post-CI follow-ups (Cosetti et al., 2010; Sawaf et al., 2022), the number of studies reporting the prognostic value of eCAP to speech perception outcomes is limited. Of the 10 included publications on children with SNHL (Cosetti et al., 2010; Motasaddi Zarandy et al., 2018), ANSD (Attias et al., 2017; Buchman et al., 2011; Jeong and Kim, 2013a; Teagle et al., 2010), and CND (Buchman et al., 2011; Song et al., 2010; Valero et al., 2012), the findings of half of the studies did not support the prognostic value of eCAP for CI outcomes (Attias et al., 2017; Cosetti et al., 2010; Fulmer et al., 2011; Motasaddi Zarandy et al., 2018; Song et al., 2010). For example, in the Cosetti et al. study (2010) on children with SNHL, predicted NRT (tNRT), representing amplitude growth function per electrode, was not correlated with open-set speech performance tests 12 months post-CI. A similar finding was reported by Morasaddi et al. (2018) on NRT hearing thresholds. Likewise, in the Attias et al. study (2017) on children with isolated ANSD (without additional disabilities or comorbidities) and a matched control group with

SNHL, despite reduced NRT electric thresholds (T), comfortable levels (C), dynamic range (DR), and tNRT in children with ANSD relative to peers with SNHL, the two groups were similar in auditory and speech recognition test scores in both quiet and noise. In the Folmer et al. (2011) study on children with ANSD, who had comorbidities, and matched control peers, the two groups were similar in eCAP recovery rate and speech recognition threshold (SRTs). Similarly in the Song et al. (2010) study on children with CND, the rate of recording stable eCAP in intraoperative and postoperative measures was not representative of speech perception scores (Song et al., 2010).

In contrast, in five studies, the eCAP findings were associated with speech performance outcomes (Buchman et al., 2011; Guedes et al., 2007; Jeong and Kim, 2013a; Teagle et al., 2010; Valero et al., 2012). In two of the studies, children with robust eCAP responses had better speech perception scores (Guedes et al., 2007; Jeong and Kim, 2013a). In the Valero et al. (2012) study on children with CND (hypoplasia), eCAP and speech perception performance were monitored at CI activation and every three months up to 24 months. Initial eCAPs were mostly absent and showed no improvement in post-CI measurements, corresponding with no improvement in speech performance scores in subsequent follow-ups. Buchman et al. (2011), also, compared the rates of recording eCAP and speech perception scores in three groups of children identified with incomplete partition-enlarged vestibular aqueduct (IP-EVA), hypoplastic malformations, and CND. Open-set speech perception was achieved in all children with IP-EVA, half of the children with hypoplastic malformations, and 19% of children with CND, and eCAP was absent in 61%, 33%, and 4% of children, respectively. Overall, robust eCAP recording was associated with higher speech perception scores, and non-oral communication strategies were more common in children with hypoplastic malformations (69%) and CND (95%) compared to children with IP-EVA (18%). In another study from the same research group on children with ANSD who had comorbidities

(42% with prematurity), only half of the children demonstrated open-set speech perception abilities, and robust eCAP responses were a predictor of open-set speech perception scores (Teagle et al., 2010). Similarly, in the Jeong and Kim (2013) study on children with ANSD, robust eCAP recording was associated with good speech performance scores.

eCAP represents the synchronous firing of a population of electrically stimulated auditory nerve fibers (He et al., 2017). Given the lesion site in ANSD, particularly in children who were diagnosed with CND, the likelihood of abnormal or absent eCAP is greater compared to children with SNHL (Moser and Starr, 2016). Extensive studies have shown that the long-term use of CIs leads to plasticity in auditory neural pathways and brain cortical areas involved in spoken language processing (Kral and Sharma, 2012; Ramsden, 2002), and children with ANSD can achieve open-speech performance scores similar to their peers with SNHL (Bo et al., 2022; Myers and Nicholson, 2021; Peng et al., 2017). This evidence refers to the idea that very early auditory electrophysiologic responses (i.e., eCAP) might not be a good representation of the level of neural plasticity in auditory pathways and speech-related cortical areas subsequent to long-term electric stimulation, which could lead to improvement in speech performance scores. This possibility could be an explanation for the inconsistency in eCAP findings in this review, at least partly. Future longitudinal eCAP studies with sufficient power may provide further clarity in this regard.

Prognostic Value of eABR Findings for CI Outcomes

EABR is a diagnostic electrophysiologic test that is defined by three positive peaks (i.e., eII, eIII, and eV) that are generated from the auditory nerve, cochlear nucleus, and neurons in the lateral lemniscus or inferior colliculus, respectively. Compared to acoustic ABR, eABR is characterized by larger amplitudes, shorter latencies, and a steeper latency-intensity function

(Firszt et al., 2002; Gordon et al., 2006). Wave I is usually hidden by stimulus artifacts and preamplifier distortion (Nada et al., 2022). Pre-operative eABR is traditionally used 1) to determine whether the CN is electrically excitable, 2) to identify which ear is the most appropriate ear for implantation, 3) to characterize the lesion site in ANSD, and 4) to provide clinicians with information about the prognosis of CIs (Gibson and Sanli, 2000; Kim et al., 2008).

In the present systematic review, all (Gibson et al., 2009; Jeon et al., 2013; Jin et al., 2013; Kim et al., 2008; Song et al., 2010; Valero et al., 2012; Walton et al., 2008; Wang et al., 2015; Yamazaki et al., 2015) but one (Jeong and Kim, 2013a) of the 11 studies reporting eABR results on diverse groups of children with CIs were indicative of the relevance of eABR findings to speech perception outcomes irrespective of the lesion site. For example, in 4 studies, a significant correlation was found between eV threshold and/or amplitude and speech recognition scores (Wang et al., 2015), or speech perception scores were reduced in those with absent or severely abnormal eABR results (Gibson et al., 2009; Nada et al., 2022; Song et al., 2010; Walton et al., 2008). Likewise, studies on children with ANSD, in particular with evidence of CND, and in a study on children with CVN abnormalities (Kim et al., 2008), absent or abnormal eV (e.g., severely delayed (Valero et al., 2012; Yamazaki et al., 2015) and increased threshold (Jin et al., 2013; Kim et al., 2008) were predictive of poor or low speech performance outcomes. Overall, it can be concluded that current evidence is supportive of the prognostic value of eABR to post-CI speech perception performance outcomes. In addition, this finding supports that compared to eCAP, eV, which is recorded from higher parts of the auditory brainstem, can better reflect the occurrence of neural plasticity in auditory pathways and cortical areas subsequent to long-term electric amplification.

Prognostic Value of MRI Findings to CI Outcomes

The clinical diagnosis of ANSD is based on a) objective electrophysiological measures of cochlear hair cells and auditory nerve function, b) imaging of CN and brainstem, and c) behavioral audiological assessments (Hall, 2015; Rance and Starr, 2015). Approximately one-third of children with ANSD are identified with CND (i.e., aplasia or hypoplasia) (Casselman et al., 1997; Hall, 2015; Roche et al., 2010). Children with CND often present with associated labyrinthine abnormalities, with widely varying degrees of severity (Peng et al., 2017). Moreover, they are at a higher risk for intracranial abnormalities and deficits in the central nervous system (CNS) (Hall, 2015). Based on MRI results, the CN is considered normal if it is the same size or larger than FN (Casselman et al., 1997). The CN is deficient if it is smaller than FN (i.e., hypoplasia). In this case, the nerve may be described as small (reduced size) or rudimentary (unbranched CVN complex). The nerve is considered absent (aplasia) if it is not seen on axial, coronal, or sagittal images (Glastonbury et al., 2002). In addition, the cochlear nerve canal (CNC) is characterized as "normal" if the vertical or transverse diameter is 4 mm or more (Glastonbury et al., 2002), "narrow" if the diameter is 2 to 3 mm (Jackler et al., 1987), and "stenotic" if the diameter is less than 2mm (Valvassori and Pierce, 1964). Measurements are taken from the narrowest portion of the CNC. Overall, the results may be surprisingly good if functioning CN fibers are displaced onto the adjacent vestibular nerve or facial FN (Wolfe, 2020).

In the present review, the findings of all 11 included studies on children with, CND (Birman et al., 2016; Chao et al., 2016; Chung et al., 2018; Han et al., 2019; Jeong and Kim, 2013a; Valero et al., 2012; Yamazaki et al., 2015), ANSD (Teagle et al., 2010), or other CVN abnormalities (Gaurav and Rajguru, 2019; Jeong and Kim, 2015; Kari et al., 2022) provide evidence of the prognostic value of MRI for CI outcomes. For instance, in children with CND, a

smaller diameter of CN compared to FN (Birman et al., 2016; Chao et al., 2016; Chung et al., 2018; Jeong and Kim, 2013a; Valero et al., 2012; Yamazaki et al., 2015) and a smaller area ratio of CVN to FN at the cerebellopontine angle (CPA) (Han et al., 2019) were associated with lower scores on speech perception tests and/or related questionnaires. In a recent study by Kari et al. (2022) on children with CVN abnormalities, among various potential contributing factors, health status, IAC midpoint diameter, and the number of nerves in the IAC were predictors of aided hearing thresholds and SATs. After adjusting the statistical analysis for health status (comorbidities or additional disabilities), the contribution of the IAC midpoint diameter and the number of nerves in the IAC to implantation outcomes remained significant (Kari et al., 2022). In another study, MRI abnormalities (i.e., demyelination of white matter of the brain, Mondini's dysplasia, communicating hydrocephalus, asymmetrical cochlear size, and features of mastoiditis) were associated with lower speech perception outcomes 12 months post-CI (Gaurav and Rajguru, 2019). In summary, according to MRI findings, although children with CND or abnormal CVN can benefit and, at times, achieve open-set speech recognition with CIs, those with hypoplasia tend to achieve better speech performance outcomes relative to those with aplasia. In fact, compared to hypoplasia, children with aplasia are more likely to receive little or no benefit from a CI (Peng et al., 2017; Vesseur et al., 2018).

It should be noted that despite the relevance of eABR and MRI findings to speech perception abilities, the studies included in this systematic review reported remarkable variability of outcomes among children with CND and CVN abnormalities (Bo et al., 2022; Peng et al., 2017; Vesseur et al., 2018). In this regard, evidence of CND or CVN abnormalities, especially the absence of CN on MRI may not entirely rule out the benefit of CIs. For example, in Yamazaki et al. (2015) study, in a series of 19 children with CND, one child with no eABR achieved a CAP

score of six. This finding suggests that the functional capacity of an abnormal CN may not be completely appreciated with current neuroimaging and electrophysiologic technology, and serves as a reminder that it is important to consider other contributing factors to CI outcomes. Regarding the latter point, in addition to the lesion site, several other factors can influence spoken language development (e.g., developmental delay, additional disabilities or comorbidities, socioeconomic status, the linguistic capacity of the family, age at implantation, duration of CI, and maternal education), however, their role was not considered in most studies reviewed or their impacts were not adjusted in the statistical analysis. These confounding factors can significantly impact the overall language development of children with severe to profound hearing loss (Bo et al., 2022; Wolfe, 2020), and their contribution to CI outcomes needs to be considered in future studies.

The follow-up period is another key contributing factor to CI outcomes. Long-term monitoring of eABR has shown evidence of plasticity (reduced latency and decreased amplitude) in the auditory brainstem (Gordon et al., 2003), which may result from improved synaptic efficacy or myelination (Nada et al., 2022). In this review, the follow-up periods varied widely both within the study population in every single study and among the included studies, which could be an important source of variability in electrophysiologic results and CI outcomes resulting in inconsistency in the literature.

The diagnosis of severe to profound SNHL can be both devastating and confusing for many parents, particularly children who are diagnosed with CND and CVN abnormalities and/or with additional disabilities or comorbid conditions. Families require substantial counseling regarding the implications of these special conditions on spoken language development, and their expectations need to be managed carefully. Moreover, the MRI and electrophysiologic results need to be taken into account carefully when making recommendations to families on what intervention

is most appropriate, especially for children with aplasia for whom expectations for spoken language are low (Kari et al., 2022).

Cross-Modal Plasticity and Poor Speech Perception Outcomes

Early sensory deprivation can lead to massive brain reorganization due to compensatory and cross-modal plasticity (Merabet and Pascual-Leone, 2010). Neurodevelopmental studies in infants with severe to profound hearing loss underline a time limit below age 4 years, and especially the first two years of life, as the sensitive period for spoken language development, in which the central auditory system exhibits its maximum plasticity (Kral and Sharma, 2012; Sharma and Campbell, 2011). Early severe to profound SNHL drives drastic intra-modal changes that severely degrade the acuity of auditory signals leading to anatomical and functional changes in sensory-deprived primary and secondary auditory areas (Finkl et al., 2020) and spoken language-related brain regions (Kral et al., 2019; Kral et al., 2017). In children with severe to profound SNHL, functional neuroimaging evidence indicates the response of the auditory regions (e.g., Heschl's gyrus, superior temporal gyrus, and planum temporale) to stimuli from intact modalities, particularly vision and tactile, as compensatory mechanisms (Almeida et al., 2015; Benetti et al., 2018; Buckley and Tobey, 2011; Ding et al., 2015; Karns et al., 2012; Li et al., 2015; Sadato et al., 2005; Shiell et al., 2016; Smith et al., 2011). The extent of this cross-modal plasticity depends on the onset age and duration of auditory deprivation (Li et al., 2013). In addition, according to functional resting-state neuroimaging studies, recording a high level of spontaneous neural activity from auditory cortical areas before CI is evidence of occupied auditory and language brain areas with other sensory modalities and is a predictor of poor CI outcomes (Lee et al., 2007). In children with CND, especially those with aplasia and other brain abnormalities, because of neural damage leading to unsuccessful use of hearing aids and possibly a higher degree of auditory deprivation

before receiving CIs, a higher extent of cross-modal plasticity is expected to contribute to poor CI outcomes for spoken language.

Study Limitations and Directions for Future Research

In this systematic review, there was substantial heterogeneity among included studies in chronological age, age at CI, follow-up periods, and outcome measures that might have affected outcomes. This heterogeneity did not allow us to conduct meta-analyses, resulting in a narrative discussion and interpretation of the findings. In assessing the strength of evidence, the included studies were predominately deficient in terms of study design, sampling, data collection, and ethical considerations. Of the 25 publications reviewed, 14 had samples below 25 participants. "Small-study effects" refer to the fact that interventions with limited sample sizes (small-study bias) are susceptible to inflated effect size estimates and publication bias, and may have resulted in more extreme treatment effects (Button et al., 2013). This impact could be partly explained by lower methodological quality in small trials (Turner et al., 2013). Thus, caution should be taken in the interpretation of systematic reviews involving small studies. Although this review was primarily focused on the impact of the lesion site, several other factors might have affected the outcomes such as comorbid symptoms, additional disabilities, age at activation of CIs, using one or two CIs, duration of CI use, cognitive function, socioeconomic status, sex, and maternal education (Bo et al., 2022; Ching et al., 2013a; le Roux et al., 2016). These factors were not in the scope of the included studies and their impact was not examined. All the included publications were observational studies, 21 retrospective and 4 prospective. Observational studies are more prone to the risk of selection bias and confounding (e.g., additional disabilities, comorbid symptoms, and socioeconomic status) (Hammer et al., 2009). In addition, studies relying on retrospective chart reviews are at risk of selection bias due to factors such as inconsistency in

administrative data recording, misclassification bias in outcome events, and missing data (Norris et al., 2014; Prada-Ramallal et al., 2019), and their impact on the overall quality of the studies should be acknowledged. Taken together, prospective study designs, which allow control over confounding factors, with adequate sample sizes and sufficient power to estimate intervention effects are recommended for future research.

Conclusions

This review aimed to systematically summarize and critically appraise existing evidence on the predictive value of intraoperative and/or postoperative eCAP and eABR as well as preoperative MRI findings to post-CI speech perception performance outcomes. Of the 25 included studies, the relevance of eCAP, eABR, and MRI findings to CI outcomes in children was reported in 10, 11, and 10 studies, respectively. While the predictive value of eCAP findings for CI outcomes was uncertain, the eABR and MRI findings supported their prognostic value for post-CI speech perception outcomes. This finding may help clinicians and the CI team in the process of decision-making for CI candidacy and consultation with the family. However, due to the observational, retrospective design and limited sample sizes in most included studies, heterogeneity of the study population in individual studies and within studies, and limited control of confounding factors, caution should be practiced in the interpretation of findings.

Conflict of interest: The authors disclose no competing interests.

Acknowledgment: This systematic review was part of a Ph.D. dissertation project in Rehabilitation Sciences, the Audiology and Speech-Language Pathology Program, approved by Ottawa University, Faculty of Health Sciences, School of Rehabilitation Sciences.

Funding: This research was offered funding support from the Ontario Graduate Scholarship (OGS) and the Queen Elizabeth II Scholarships in Science and Technology (QEII-GSST).

Author Contributions: ZJ and AK conceptualized the study. ZJ wrote the first draft of the manuscript. ZJ and AK performed the systematic search, paper selection, and data extraction. All authors read and approved the publication of the final manuscript. AK provided project leadership.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author (AK).

References:

Almeida, J., He, D., Chen, Q., Mahon, B.Z., Zhang, F., Gonçalves Ó, F., Fang, F., Bi, Y. (2015). Decoding Visual Location From Neural Patterns in the Auditory Cortex of the Congenitally Deaf. *Psychol Sci*. 26(11), 1771-1782. doi:10.1177/0956797615598970.

Arjmandi, M.K., Herrmann, B.S., Caswell-Midwinter, B., Doney, E.M., Arenberg, J.G. (2022). A Modified Pediatric Ranked Order Speech Perception Score to Assess Speech Recognition Development in Children With Cochlear Implants. *Am J Audiol*. 31(3), 613-632. doi:10.1044/2022_aja-21-00212.

Attias, J., Greenstein, T., Peled, M., Ulanovski, D., Wohlgelernter, J., Raveh, E. (2017). Auditory Performance and Electrical Stimulation Measures in Cochlear Implant Recipients With Auditory Neuropathy Compared With Severe to Profound Sensorineural Hearing Loss. *Ear Hear*. 38(2), 184-193. doi:10.1097/aud.0000000000000384.

Benetti, S., Novello, L., Maffei, C., Rabini, G., Jovicich, J., Collignon, O. (2018). White matter connectivity between occipital and temporal regions involved in face and voice processing in hearing and early deaf individuals. *Neuroimage*. 179, 263-274. doi:10.1016/j.neuroimage.2018.06.044.

Birman, C.S., Powell, H.R., Gibson, W.P., Elliott, E.J. (2016). Cochlear Implant Outcomes in Cochlea Nerve Aplasia and Hypoplasia. *Otol Neurotol*. 37(5), 438-445. doi:10.1097/mao.0000000000000997.

Bo, D., Huang, Y., Wang, B., Lu, P., Chen, W.X., Xu, Z.M. (2022). Auditory and Speech Outcomes of Cochlear Implantation in Children With Auditory Neuropathy Spectrum Disorder: A Systematic Review and Meta-Analysis. *Ann Otol Rhinol Laryngol*, 34894221092201. doi:10.1177/00034894221092201.

Breneman, A.I., Gifford, R.H., Dejong, M.D. (2012). Cochlear implantation in children with auditory neuropathy spectrum disorder: long-term outcomes. *J Am Acad Audiol*. 23(1), 5-17. doi:10.3766/jaaa.23.1.2.

Buchman, C.A., Teagle, H.F., Roush, P.A., Park, L.R., Hatch, D., Woodard, J., Zdanski, C., Adunka, O.F. (2011). Cochlear implantation in children with labyrinthine anomalies and cochlear nerve deficiency: implications for auditory brainstem implantation. *Laryngoscope*. 121(9), 1979-1988. doi:10.1002/lary.22032.

Buckley, K.A., Tobey, E.A. (2011). Cross-modal plasticity and speech perception in pre- and postlingually deaf cochlear implant users. *Ear Hear*. 32(1), 2-15. doi:10.1097/AUD.0b013e3181e8534c.

Button, K.S., Ioannidis, J.P., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S., Munafò, M.R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci*. 14(5), 365-376. doi:10.1038/nrn3475.

Casselman, J.W., Offeciers, F.E., Govaerts, P.J., Kuhweide, R., Geldof, H., Somers, T., D'Hont, G. (1997). Aplasia and hypoplasia of the vestibulocochlear nerve: diagnosis with MR imaging. *Radiology*. 202(3), 773-781. doi:10.1148/radiology.202.3.9051033.

Chao, X., Luo, J., Fan, Z., Shi, H., Han, Y., Wang, R., Song, Y., Wang, G., Wang, H., Xu, L. (2016). Usefulness of radiological findings for predicting cochlear implantation outcomes in children with cochlear nerve deficiency: a pilot study. *Acta Otolaryngol*. 136(10), 1051-1057. doi:10.1080/00016489.2016.1179788.

Chaudhry, D., Chaudhry, A., Muzaffar, J., Monksfield, P., Bance, M. (2020). Cochlear Implantation Outcomes in Post Synaptic Auditory Neuropathies: A Systematic Review and Narrative Synthesis. *J Int Adv Otol*. 16(3), 411-431. doi:10.5152/iao.2020.9035.

Ching, T.Y., Day, J., Dillon, H., Gardner-Berry, K., Hou, S., Seeto, M., Wong, A., Zhang, V. (2013a). Impact of the presence of auditory neuropathy spectrum disorder (ANSD) on outcomes of children at three years of age. *Int J Audiol*. 52 Suppl 2(0 2), S55-64. doi:10.3109/14992027.2013.796532.

Ching, T.Y., Dillon, H., Marnane, V., Hou, S., Day, J., Seeto, M., Crowe, K., Street, L., Thomson, J., Van Buynder, P., Zhang, V., Wong, A., Burns, L., Flynn, C., Cupples, L., Cowan, R.S., Leigh, G., Sjahalam-King, J., Yeh, A. (2013b). Outcomes of early- and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear Hear*. 34(5), 535-552. doi:10.1097/AUD.0b013e3182857718.

Chung, J., Jang, J.H., Chang, S.O., Song, J.J., Cho, S.W., Kim, S.Y., Lee, J.H., Oh, S.H. (2018). Does the Width of the Bony Cochlear Nerve Canal Predict the Outcomes of Cochlear Implantation? *Biomed Res Int*. 2018, 5675848. doi:10.1155/2018/5675848.

Cosetti, M.K., Shapiro, W.H., Green, J.E., Roman, B.R., Lalwani, A.K., Gunn, S.H., Roland, J.T., Jr., Waltzman, S.B. (2010). Intraoperative neural response telemetry as a predictor of performance. *Otol Neurotol*. 31(7), 1095-1099. doi:10.1097/MAO.0b013e3181ec1b8c.

Crowe, M., Sheppard, L. (2011). A general critical appraisal tool: an evaluation of construct validity. *Int J Nurs Stud*. 48(12), 1505-1516. doi:10.1016/j.ijnurstu.2011.06.004.

Crowe, M., Sheppard, L., Campbell, A. (2012). Reliability analysis for a proposed critical appraisal tool demonstrated value for diverse research designs. *J Clin Epidemiol*. 65(4), 375-383. doi:10.1016/j.jclinepi.2011.08.006.

Cupples, L., Ching, T.Y.C., Button, L., Leigh, G., Marnane, V., Whitfield, J., Gunnourie, M., Martin, L. (2018). Language and speech outcomes of children with hearing loss and additional disabilities: identifying the variables that influence performance at five years of age. *Int J Audiol*. 57(sup2), S93-s104. doi:10.1080/14992027.2016.1228127.

Ding, H., Qin, W., Liang, M., Ming, D., Wan, B., Li, Q., Yu, C. (2015). Cross-modal activation of auditory regions during visuospatial working memory in early deafness. *Brain*. 138(Pt 9), 2750-2765. doi:10.1093/brain/awv165.

Dutt, S.N., Kumar, A., Mittal, A.A., Vadlamani, S., Gaur, S.K. (2021). Cochlear implantation in auditory neuropathy spectrum disorders: role of transtympanic electrically evoked auditory brainstem responses and serial neural response telemetry. *J Laryngol Otol*. 135(7), 602-609. doi:10.1017/s0022215121001328.

Finkl, T., Hahne, A., Friederici, A.D., Gerber, J., Mürbe, D., Anwander, A. (2020). Language Without Speech: Segregating Distinct Circuits in the Human Brain. *Cereb Cortex*. 30(2), 812-823. doi:10.1093/cercor/bhz128.

Firszt, J.B., Chambers, R.D., Kraus, Reeder, R.M. (2002). Neurophysiology of cochlear implant users I: effects of stimulus current level and electrode site on the electrical ABR, MLR, and N1-P2 response. *Ear Hear*. 23(6), 502-515. doi:10.1097/00003446-200212000-00002.

Fulmer, S.L., Runge, C.L., Jensen, J.W., Friedland, D.R. (2011). Rate of neural recovery in implanted children with auditory neuropathy spectrum disorder. *Otolaryngol Head Neck Surg*. 144(2), 274-279. doi:10.1177/0194599810391603.

Gaurav, V., Rajguru, T. (2019). Effects of radiological abnormalities in temporal bone and brain on auditory outcomes in cochlear implant recipient children. *Indian J Otol*. 25, 85-89.

Gibson, W., Sanli, H., 2000. The role of round window electrophysiological techniques in the selection of children for cochlear implants. In: Kim, C., Chang, S., Lim, D. (Eds.), Advances in Oto-Rhino-Laryngology. Karger, Basel, pp. 148-151.

Gibson, W.P., Sanli, H. (2007). Auditory neuropathy: an update. *Ear Hear*. 28(2 Suppl), 102s-106s. doi:10.1097/AUD.0b013e3180315392.

Gibson, W.P., Sanli, H., Psarros, C. (2009). The use of intra-operative electrical auditory brainstem responses to predict the speech perception outcome after cochlear implantation. *Cochlear Implants Int*. 10 Suppl 1, 53-57. doi:10.1179/cim.2009.10.Supplement-1.53.

Glastonbury, C.M., Davidson, H.C., Harnsberger, H.R., Butler, J., Kertesz, T.R., Shelton, C. (2002). Imaging findings of cochlear nerve deficiency. *AJNR Am J Neuroradiol*. 23(4), 635-643.

Gordon, K.A., Papsin, B.C., Harrison, R.V. (2003). Activity-dependent developmental plasticity of the auditory brainstem in children who use cochlear implants. *Ear Hear*. 24(6), 485-500. doi:10.1097/01.aud.0000100203.65990.d4.

Gordon, K.A., Papsin, B.C., Harrison, R.V. (2006). An evoked potential study of the developmental time course of the auditory nerve and brainstem in children using cochlear implants. *Audiol Neurootol*. 11(1), 7-23. doi:10.1159/000088851.

Guedes, M.C., Weber, R., Gomez, M.V., Neto, R.V., Peralta, C.G., Bento, R.F. (2007). Influence of evoked compound action potential on speech perception in cochlear implant users. *Braz J Otorhinolaryngol*. 73(4), 439-445. doi:10.1016/s1808-8694(15)30095-1.

Guyatt, G.H., Oxman, A.D., Vist, G.E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H.J. (2008). GRADE: An emerging consensus on rating the quality of evidence and strength of recommendations. *BMJ*. 336(7650), 924-926. doi:10.1136/bmj.39489.470347.AD.

Hall, J., 2015. eHandbook of Auditory Evoked Responses: Principles, Procedures & Protocols. Pearson Education, Inc.

Hammer, G.P., du Prel, J.B., Blettner, M. (2009). Avoiding bias in observational studies: part 8 in a series of articles on evaluation of scientific publications. *Dtsch Arztebl Int*. 106(41), 664-668. doi:10.3238/arztebl.2009.0664.

Han, J.J., Suh, M.W., Park, M.K., Koo, J.W., Lee, J.H., Oh, S.H. (2019). A Predictive Model for Cochlear Implant Outcome in Children with Cochlear Nerve Deficiency. *Sci Rep*. 9(1), 1154. doi:10.1038/s41598-018-37014-7.

He, S., Teagle, H.F.B., Buchman, C.A. (2017). The Electrically Evoked Compound Action Potential: From Laboratory to Clinic. *Front Neurosci*. 11, 339. doi:10.3389/fnins.2017.00339.

Jackler, R.K., Luxford, W.M., House, W.F. (1987). Congenital malformations of the inner ear: a classification based on embryogenesis. *Laryngoscope*. 97(3 Pt 2 Suppl 40), 2-14. doi:10.1002/lary.5540971301.

Jafari, Z., Kolb, B.E., Mohajerani, M.H. (2021). Hearing Loss, Tinnitus, and Dizziness in COVID-19: A Systematic Review and Meta-Analysis. *Can J Neurol Sci*, 1-12. doi:10.1017/cjn.2021.63.

JCIH. (2019). Year 2019 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs. *The Journal of Early Hearing Detection and Intervention*. 4(2), 1-44.

Jeon, J.H., Bae, M.R., Song, M.H., Noh, S.H., Choi, K.H., Choi, J.Y. (2013). Relationship between electrically evoked auditory brainstem response and auditory performance after cochlear implant in patients with auditory neuropathy spectrum disorder. *Otol Neurotol*. 34(7), 1261-1266. doi:10.1097/MAO.0b013e318291c632.

Jeong, S.W., Kim, L.S. (2013a). Auditory neuropathy spectrum disorder: predictive value of radiologic studies and electrophysiologic tests on cochlear implant outcomes and its radiologic classification. *Acta Otolaryngol*. 133(7), 714-721. doi:10.3109/00016489.2013.776176.

Jeong, S.W., Kim, L.S. (2013b). Auditory neuropathy spectrum disorder: Predictive value of radiologic studies and electrophysiologic tests on cochlear implant outcomes and its radiologic classification. *Acta Oto-Laryngologica*. 133(7), 714-721. doi:10.3109/00016489.2013.776176.

Jeong, S.W., Kim, L.S. (2015). A new classification of cochleovestibular malformations and implications for predicting speech perception ability after cochlear implantation. *Audiol Neurootol*. 20(2), 90-101. doi:10.1159/000365584.

Jin, Y., Cao, K., Wei, C., Wang, B. (2013). [Evaluation of intra-operative EABR characteristics and rehabilitation effects of cochlear implantation in patients with internal auditory canal stenosis]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 27(13), 694-697, 700.

Kandel, E., Koester, D., Mack, S., Siegelbaum, S., 2021. Principles of Neural Science, Sixth Edition ed. McGraw Hill, New York.

Kari, E., Gillard, D.M., Chuang, N., Go, J.L. (2022). Can Imaging Predict Hearing Outcomes in Children With Cochleovestibular Nerve Abnormalities? *Laryngoscope*. 132 Suppl 8, S1-s15. doi:10.1002/lary.30008.

Karns, C.M., Dow, M.W., Neville, H.J. (2012). Altered cross-modal processing in the primary auditory cortex of congenitally deaf adults: a visual-somatosensory fMRI study with a double-flash illusion. *J Neurosci*. 32(28), 9626-9638. doi:10.1523/jneurosci.6488-11.2012.

Kim, A.H., Kileny, P.R., Arts, H.A., El-Kashlan, H.K., Telian, S.A., Zwolan, T.A. (2008). Role of electrically evoked auditory brainstem response in cochlear implantation of children with inner ear malformations. *Otol Neurotol*. 29(5), 626-634. doi:10.1097/MAO.0b013e31817781f5.

Kim, J.R., Kim, L.S., Jeong, S.W., Kim, J.S., Chung, S.H. (2011). Recovery function of electrically evoked compound action potential in implanted children with auditory neuropathy: preliminary results. *Acta Otolaryngol*. 131(8), 796-801. doi:10.3109/00016489.2011.560187.

Kral, A., Dorman, M.F., Wilson, B.S. (2019). Neuronal Development of Hearing and Language: Cochlear Implants and Critical Periods. *Annu Rev Neurosci*. 42, 47-65. doi:10.1146/annurev-neuro-080317-061513.

Kral, A., Sharma, A. (2012). Developmental neuroplasticity after cochlear implantation. *Trends Neurosci*. 35(2), 111-122. doi:10.1016/j.tins.2011.09.004.

Kral, A., Yusuf, P.A., Land, R. (2017). Higher-order auditory areas in congenital deafness: Top-down interactions and corticocortical decoupling. *Hear Res*. 343, 50-63. doi:10.1016/j.heares.2016.08.017.

Kuchta, J. (2007). Twenty-five years of auditory brainstem implants: perspectives. *Acta Neurochir Suppl*. 97(Pt 2), 443-449. doi:10.1007/978-3-211-33081-4_51.

le Roux, T., Vinck, B., Butler, I., Cass, N., Louw, L., Nauta, L., Schlesinger, D., Soer, M., Tshifularo, M., Swanepoel de, W. (2016). Predictors of pediatric cochlear implantation outcomes in South Africa. *Int J Pediatr Otorhinolaryngol*. 84, 61-70. doi:10.1016/j.ijporl.2016.02.025.

Lee, H.J., Giraud, A.L., Kang, E., Oh, S.H., Kang, H., Kim, C.S., Lee, D.S. (2007). Cortical activity at rest predicts cochlear implantation outcome. *Cereb Cortex*. 17(4), 909-917. doi:10.1093/cercor/bhl001.

Leigh, J., Dettman, S., Dowell, R., Sarant, J. (2011). Evidence-based approach for making cochlear implant recommendations for infants with residual hearing. *Ear Hear*. 32(3), 313-322. doi:10.1097/AUD.0b013e3182008b1c.

Li, W., Li, J., Wang, Z., Li, Y., Liu, Z., Yan, F., Xian, J., He, H. (2015). Grey matter connectivity within and between auditory, language and visual systems in prelingually deaf adolescents. *Restor Neurol Neurosci*. 33(3), 279-290. doi:10.3233/rnn-140437.

Li, Y., Booth, J.R., Peng, D., Zang, Y., Li, J., Yan, C., Ding, G. (2013). Altered intra- and inter-regional synchronization of superior temporal cortex in deaf people. *Cereb Cortex*. 23(8), 1988-1996. doi:10.1093/cercor/bhs185.

Lim, H.H., Lenarz, M., Lenarz, T. (2009). Auditory midbrain implant: a review. *Trends Amplif*. 13(3), 149-180. doi:10.1177/1084713809348372.

Madden, C., Rutter, M., Hilbert, L., Greinwald, J.H., Jr., Choo, D.I. (2002). Clinical and audiological features in auditory neuropathy. *Arch Otolaryngol Head Neck Surg*. 128(9), 1026-1030. doi:10.1001/archotol.128.9.1026.

Mason, J.C., De Michele, A., Stevens, C., Ruth, R.A., Hashisaki, G.T. (2003). Cochlear implantation in patients with auditory neuropathy of varied etiologies. *Laryngoscope*. 113(1), 45-49. doi:10.1097/00005537-200301000-00009.

Merabet, L.B., Pascual-Leone, A. (2010). Neural reorganization following sensory loss: the opportunity of change. *Nat Rev Neurosci*. 11(1), 44-52. doi:10.1038/nrn2758.

Morgan, R.L., Whaley, P., Thayer, K.A., Schünemann, H.J. (2018). Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int*. 121(Pt 1), 1027-1031. doi:10.1016/j.envint.2018.07.015.

Moser, T., Starr, A. (2016). Auditory neuropathy--neural and synaptic mechanisms. *Nat Rev Neurol*. 12(3), 135-149. doi:10.1038/nrneurol.2016.10.

Motasaddi Zarandy, M., Nourizadeh, N., Mobedshahi, F., Jafarzadeh, S. (2018). Relationship between Electrically Evoked Compound Action Potential Thresholds and Auditory, Language, and Speech Progress after Cochlear Implant Surgery. *Iran J Otorhinolaryngol*. 30(99), 185-188.

Murad, M.H., Mustafa, R.A., Schünemann, H.J., Sultan, S., Santesso, N. (2017). Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 22(3), 85-87. doi:10.1136/ebmed-2017-110668.

Myers, K., Nicholson, N. (2021). Cochlear Implant Behavioral Outcomes for Children With Auditory Neuropathy Spectrum Disorder: A Mini-Systematic Review. *Am J Audiol*. 30(3), 777-789. doi:10.1044/2021_aja-20-00175.

Nada, N., Kolkaila, E., Schendzielorz, P., El Mahallawi, T. (2022). Electrically evoked auditory brainstem response in cochlear implantation: what you need to know (short review). *The Egyptian Journal of Otolaryngology*. 38(67), 1-8. doi:doi.org/10.1186/s43163-022-00259-1.

Nikolopoulos, T.P., Mason, S.M., Gibbin, K.P., O'Donoghue, G.M. (2000). The prognostic value of promontory electric auditory brain stem response in pediatric cochlear implantation. *Ear Hear*. 21(3), 236-241. doi:10.1097/00003446-200006000-00007.

Niparko, J.K., Tobey, E.A., Thal, D.J., Eisenberg, L.S., Wang, N.Y., Quittner, A.L., Fink, N.E. (2010). Spoken language development in children following cochlear implantation. *Jama*. 303(15), 1498-1506. doi:10.1001/jama.2010.451.

Norris, S., D., A., Bruening, W., Fox, S., Johnson, E., Kane, R., Morton, S., Oremus, M., Ospina, M., Randhawa, G., Schoelles, K., Sjhekelle, P., Viswanathan, M., 2014. Assessing the Risk of Bias in Systematic Reviews of Health Care Interventions. In: Kronick, R., Slutsky, J., Chang, S. (Eds.), Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality (US), Rockville (MD), pp. 180-192..

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P.,

Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 134, 178-189. doi:10.1016/j.jclinepi.2021.03.001.

Peng, K.A., Kuan, E.C., Hagan, S., Wilkinson, E.P., Miller, M.E. (2017). Cochlear Nerve Aplasia and Hypoplasia: Predictors of Cochlear Implant Success. *Otolaryngol Head Neck Surg*. 157(3), 392-400. doi:10.1177/0194599817718798.

Prada-Ramallal, G., Takkouche, B., Figueiras, A. (2019). Bias in pharmacoepidemiologic studies using secondary health care databases: a scoping review. *BMC Med Res Methodol*. 19(1), 53. doi:10.1186/s12874-019-0695-y.

Rajput, K., Saeed, M., Ahmed, J., Chung, M., Munro, C., Patel, S., Leal, C., Jiang, D., Nash, R. (2019). Findings from aetiological investigation of Auditory Neuropathy Spectrum Disorder in children referred to cochlear implant programs. *Int J Pediatr Otorhinolaryngol*. 116, 79-83. doi:10.1016/j.ijporl.2018.10.010.

Ramsden, R.T. (2002). Cochlear implants and brain stem implants. *Br Med Bull*. 63, 183-193. doi:10.1093/bmb/63.1.183.

Rance, G., Barker, E.J. (2009). Speech and language outcomes in children with auditory neuropathy/dys-synchrony managed with either cochlear implants or hearing aids. *Int J Audiol*. 48(6), 313-320. doi:10.1080/14992020802665959.

Rance, G., Starr, A. (2015). Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. *Brain*. 138(Pt 11), 3141-3158. doi:10.1093/brain/awv270.

Roche, J.P., Huang, B.Y., Castillo, M., Bassim, M.K., Adunka, O.F., Buchman, C.A. (2010). Imaging characteristics of children with auditory neuropathy spectrum disorder. *Otol Neurotol*. 31(5), 780-788. doi:10.1097/mao.0b013e3181d8d528.

Roush, P., Frymark, T., Venediktov, R., Wang, B. (2011). Audiologic management of auditory neuropathy spectrum disorder in children: a systematic review of the literature. *Am J Audiol*. 20(2), 159-170. doi:10.1044/1059-0889(2011/10-0032).

Sadato, N., Okada, T., Honda, M., Matsuki, K., Yoshida, M., Kashikura, K., Takei, W., Sato, T., Kochiyama, T., Yonekura, Y. (2005). Cross-modal integration and plastic changes revealed by lip movement, random-dot motion and sign languages in the hearing and deaf. *Cereb Cortex*. 15(8), 1113-1122. doi:10.1093/cercor/bhh210.

Santarelli, R., Rossi, R., Scimemi, P., Cama, E., Valentino, M.L., La Morgia, C., Caporali, L., Liguori, R., Magnavita, V., Monteleone, A., Biscaro, A., Arslan, E., Carelli, V. (2015). OPA1-related auditory neuropathy: site of lesion and outcome of cochlear implantation. *Brain*. 138(Pt 3), 563-576. doi:10.1093/brain/awu378.

Santarelli, R., Scimemi, P., La Morgia, C., Cama, E., Del Castillo, I., Carelli, V. (2021). Electrocochleography in Auditory Neuropathy Related to Mutations in the OTOF or OPA1 Gene. *Audiol Res*. 11(4), 639-652. doi:10.3390/audiolres11040059.

Sawaf, T., Vovos, R., Hadford, S., Woodson, E., Anne, S. (2022). Utility of intraoperative neural response telemetry in pediatric cochlear implants. *Int J Pediatr Otorhinolaryngol*. 162, 111298. doi:10.1016/j.ijporl.2022.111298.

Schünemann, H., Brożek, J., Guyatt, G., Oxman, A., 2013. GRADE Handbook. GRADE Working Group.

Shallop, J. (2002). Auditory neuropathy/dys-synchrony in adults and children. *Sem Hear*(23), 215-223.

Sharma, A., Campbell, J. (2011). A sensitive period for cochlear implantation in deaf children. *J Matern Fetal Neonatal Med*. 24 Suppl 1(0 1), 151-153. doi:10.3109/14767058.2011.607614.

Shearer, A.E., Hansen, M.R. (2019). Auditory synaptopathy, auditory neuropathy, and cochlear implantation. *Laryngoscope Investig Otolaryngol*. 4(4), 429-440. doi:10.1002/lio2.288.

Shiell, M.M., Champoux, F., Zatorre, R.J. (2016). The Right Hemisphere Planum Temporale Supports Enhanced Visual Motion Detection Ability in Deaf People: Evidence from Cortical Thickness. *Neural Plast*. 2016, 7217630. doi:10.1155/2016/7217630.

Smith, K.M., Mecoli, M.D., Altaye, M., Komlos, M., Maitra, R., Eaton, K.P., Egelhoff, J.C., Holland, S.K. (2011). Morphometric differences in the Heschl's gyrus of hearing impaired and normal hearing infants. *Cereb Cortex*. 21(5), 991-998. doi:10.1093/cercor/bhq164.

Song, M.H., Bae, M.R., Kim, H.N., Lee, W.S., Yang, W.S., Choi, J.Y. (2010). Value of intracochlear electrically evoked auditory brainstem response after cochlear implantation in patients with narrow internal auditory canal. *Laryngoscope*. 120(8), 1625-1631. doi:10.1002/lary.21008.

Starr, A., Rance, G., 2015. Auditory neuropathy. In: Celesia, G., Hickok, G. (Eds.), Handbook of Clinical Neurology. Elsevier, Edinburgh pp. 495-508.

Teagle, H.F., Roush, P.A., Woodard, J.S., Hatch, D.R., Zdanski, C.J., Buss, E., Buchman, C.A. (2010). Cochlear implantation in children with auditory neuropathy spectrum disorder. *Ear Hear*. 31(3), 325-335. doi:10.1097/AUD.0b013e3181ce693b.

Turner, R.M., Bird, S.M., Higgins, J.P. (2013). The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLoS One*. 8(3), e59202. doi:10.1371/journal.pone.0059202.

Valero, J., Blaser, S., Papsin, B.C., James, A.L., Gordon, K.A. (2012). Electrophysiologic and behavioral outcomes of cochlear implantation in children with auditory nerve hypoplasia. *Ear Hear*. 33(1), 3-18. doi:10.1097/AUD.0b013e3182263460.

Valvassori, G.E., Pierce, R.H. (1964). The Normal InternL Auditory Canal. *Am J Roentgenol Radium Ther Nucl Med*. 92, 1232-1241.

Vesseur, A., Free, R., Snels, C., Dekker, F., Mylanus, E., Verbist, B., Frijns, J. (2018). Hearing Restoration in Cochlear Nerve Deficiency: the Choice Between Cochlear Implant or Auditory Brainstem Implant, a Meta-analysis. *Otol Neurotol*. 39(4), 428-437. doi:10.1097/mao.0000000000001727.

Walton, J., Gibson, W.P., Sanli, H., Prelog, K. (2008). Predicting cochlear implant outcomes in children with auditory neuropathy. *Otol Neurotol*. 29(3), 302-309. doi:10.1097/MAO.0b013e318164d0f6.

Wang, Y., Pan, T., Deshpande, S.B., Ma, F. (2015). The Relationship Between EABR and Auditory Performance and Speech Intelligibility Outcomes in Pediatric Cochlear Implant Recipients. *Am J Audiol*. 24(2), 226-234. doi:10.1044/2015_aja-14-0023.

Wilson, B.S. (2011). A 'top down' or 'cognitive neuroscience' approach to cochlear implant designs and fittings. *Cochlear Implants Int*. 12 Suppl 1, S35-39. doi:10.1179/146701011x13001035753272.

Wilson, B.S., Dorman, M.F., Woldorff, M.G., Tucci, D.L. (2011). Cochlear implants matching the prosthesis to the brain and facilitating desired plastic changes in brain function. *Prog Brain Res*. 194, 117-129. doi:10.1016/b978-0-444-53815-4.00012-1.

Wolfe, J., 2020. Cochlear Implants: Audiologic Management and Considerations for Implantable Hearing Devices. Plural Publishing Inc., San Diego.

Yamazaki, H., Leigh, J., Briggs, R., Naito, Y. (2015). Usefulness of MRI and EABR Testing for Predicting CI Outcomes Immediately After Cochlear Implantation in Cases With Cochlear Nerve Deficiency. *Otol Neurotol*. 36(6), 977-984. doi:10.1097/mao.0000000000000721.

Zeng, F.G., Liu, S. (2006). Speech perception in individuals with auditory neuropathy. *J Speech Lang Hear Res*. 49(2), 367-380. doi:10.1044/1092-4388(2006/029).

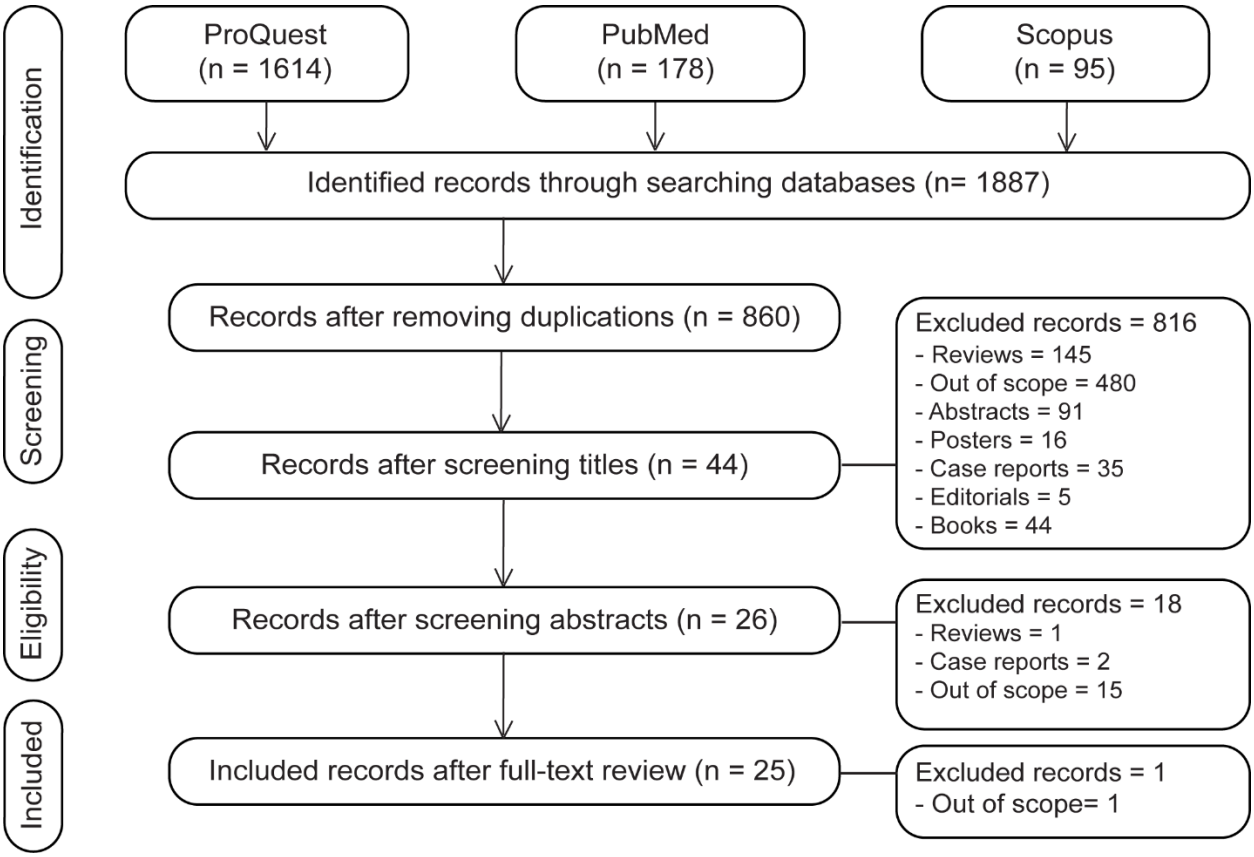

Figure 1. The PRISMA flow diagram illustrates the method used for literature search, screening, and summarizing evidence. Publications that did not meet PICOS's criteria were excluded. PICOS stands for participants, interventions, comparators, outcomes, and study designs, respectively. PRISMA: preferred reporting items for systematic reviews and meta-analyses.

Table 1. Characteristics of studies on the prognostic value of eCAP for CI outcomes

Study Country	Study design	Diagnosis	Participants	Age at CI (months)	Device	Uni/Bi	Follow-up period (months)	Electrophysiology	Outcome measures	Findings
Motasaddi Zarandy et al. 2018 Iran	Pros	SNHL	10, 3-5 years, 7 girls	50.4	Nucleus	All Uni	6	Postoperative NRT	Newsha developmental scale	Improvement in speech and language scores post-implantation despite no change in eCAP hearing thresholds.
Attias et al. 2017 Israel	Pros	ANSD Matched SNHL	ANSD: 16, 5-12.2 years, 6 girls SNHL: 16, 6.7-13.2, 8 girls	ANSD: 11-34 SNHL: 10-26	Majority with Nucleus, AB, MedEl	ANSD: 6/10 SNHL: 8/8	40	Postoperative eT, eCL, eDR, and tNRT only in Nucleus CI users	MWT, SWT, and EST in quiet and noise	Despite reduced eT, eCL, eDR, and tNRT in children with ANSD, they showed no difference with children with SNHL in speech performance outcomes.
Jeong and Kim 2013 Korea	Retro	ANSD	15, 3.5 years, 5 girls	70	Nucleus	NR	72.08	Postoperative eCAP (3 weeks postsurgery)	CAP, IT-MAIS, open-set MWT	Better speech perception abilities were observed in children with robust eCAP results.

Valero et al. 2012 Canada	Retro	CND (hypoplasia) Matched SNHL	19, 10 girls	Hypoplasia: 50.4 (12-155) SNHL: 51.24 (12-172.2)	Nucleus	Hypoplasia: 17/2 SNHL: 17/2	At CI activation and every 3 months up to 24 months	Postoperative eCAP	ESP, IT-MAIS, WIPI, GASP, MLNT, BKB words, LNT phonemes, BKB phonemes	In children with hypoplasia, initial eCAPs were mostly absent. In the first and last assessments, eCAP was recorded in 2 out of 7 and 2 out of 6 children with hypoplasia, respectively, and in 17 out of 17 control children in both assessments. Speech performance, the PROSPER scores,[b] was lower in both initial and the most recent assessments and did not improve over time.
Buchman et al. 2011 USA	Retro	Inner ear malformation or CND with AD/C	76, 46% girls. CND: 22 Non-CND: 54	72.0 (15.6-216)	Nucleus, AB	64/12	12-120	Intraoperative NRT	SRI-Q, ESP, PBK, CNC words	Open-set speech perception was achieved in 100% of children with IP-EVA, 50% of children with hypoplastic malformations, and 19%

										of children with CND. eCAP was absent in 61%, 33%, and 4% of children with CND, hypoplastic malformations, and IP-EVA, respectively. Robust eCAP recording was associated with higher speech perception scores. Manual communication was more common in children with hypoplastic malformations (69%) and CND (95%) compared to those with IP-EVA (18%).
Fulmer et al. 2011 USA	Retro	ANSD with comorbidities[a]	ANSD: 10 SNHL: 10	ANSD: 44.4 SNHL: 58.8	Nucleus, AB, MedEl	ANSD : 8/2 SNHL : 6/4	ANSD: 43.2 SNHL: 51.6	Postoperative eCAP	SRT for monosyllabic and spondee words	Children with ANSD and SNHL were not different in SRT and eCAP recovery rates.

		Matched SNHL								
Cosetti et al. 2010 USA	Retro	SNHL	24, 5-17 years	Children: 7.5 years	Nucleus	NR	12	Intraoperative tNRT	Children: MLNT, PBK, LNT, GASP	No correlation between tNRT results and open-set speech performance.
Song et al. 2010 Korea	Retro	CND, 9 with aplasia	13, 4.3 (1-13) years,	NR	Nucleus, AB	NR	26.5 (12-68)	Intra- and postoperative eCAP at 1, 3, 6, 12, 18, and 24	CAP, IT-MAIS	The average IAC was 1.78 mm (0.75-2.57 mm). Post-CI CAP scores ranged from 0 to 4. Only 2 children showed stable eCAP responses in post-CI assessments. No correlation was found between eCAP and CAP results.
Teagle et al. 2010 USA	Retro	ANSD (6 with CND) with medical comorbidities, 42%	52, 7.3 years, 19 girls	47, 12-213	Nucleus, AB	2/50	41 (6-118)	Intraoperative eCAP	ESP, PBK, MLNT, LNT, IT-MAIS	50% demonstrated open-set speech perception abilities, and nearly 30% were unable to complete the test because of low CI experience or

		with prematurity								developmental delays. No child with CND achieved open-set speech perception abilities. In a subgroup of children with the results of eCAP and PBK tests, good open-set speech perception skills were associated with robust eCAP responses.
Guedes et al. 2007 Brazil	Retro	NR	100, 53% girls, 61 below 20 years	NR	Nucleus	NR	6	Intraoperative NRT	Hearing capacity test, GASP	NRT response was recorded in 72% of children. Open-set sentence test scores were significantly better in children with present compared to absent NRT.

AB: advanced Bionics, AD/C: additional disabilities/comorbidities, ANSD: auditory neuropathy spectrum disorder, BKB: Bamford-Kowal-Bench sentence test, CAP: Categories of Auditory Performance, CDI: child development inventory, CI: cochlear implant, CL: comfortable level, CNC: consonant-nucleus-consonant, DEAP: diagnostic evaluation of articulation and phonology, DR: dynamic range, eCAP: electric compound action potential, ESP: early speech perception, EST: everyday sentence test, GASP: Glendonald Auditory Screening Procedure, IP-EVA: incomplete partition-enlarged vestibular aqueduct, IT-MAIS: Infant-Toddler Meaningful Auditory Integration Scale, LNT: lexical neighborhood test, MLNT:

Multi-syllable Lexical Neighborhood Test, MWT: Mono-syllabic Word Test, NR: not reported, NRT: neural response telemetry, PBK: Phonetically Balanced Kindergarten, SIR: Speech Intelligibility Rating, SNHL: sensorineural hearing loss, SRI-Q: speech recognition index in quite, SP: speech perception, Pros: prospective, Retro: retrospective, SRT: speech recognition threshold, SWT: spondee word test, T: threshold, tNRT: predicted NRT, WIPI: Word Intelligibility by Picture Identification, WRS: word recognition score.

[a] Including hyperbilirubinemia, family history, premature birth, hypoxia, perinatal infection, cystic fibrosis, Mondini malformation, attention deficit hyperactivity disorder (ADHD), autism

[b] The Pediatric Ranked Order Speech Perception (PROSPER) score allows for the comparison of speech and language outcomes across varying testing conditions, both between participants and within a single participant tested repeatedly over time. In PROSPER, tests are ranked according to their relative difficulty and quantified from 0 (least complex) to 34 (most complex) (Arjmandi et al., 2022; Valero et al., 2012).

Table 2. Characteristics of studies on the prognostic value of eABR for CI outcomes

Study Country	Study design	Diagnosis	Participants	Age at CI (months)	Device	Uni/ Bi	Follow-up period (months)	Electrophysiology	Outcome measures	Findings
Wang et al. 2015 China	Retro	SNHL	40, 1.7-7.0 years, 14 girls	12-58.8	Nucleus	NR	3 to 26	Intraoperative eABR	CAP and SIR growth[c]	A correlation was found between the eV threshold and SIR growth. Children with better CAP growth had a lower eV threshold compared to those with lower CAP growth.
Yamazaki et al. 2015 Japan	Retro	CND	19	26.7 (11.5)	Nucleus	5/14	24	Intraoperative eABR[b]	CAP	Poor speech performance in children with delayed eV compared to better speech performance in children with positive eV.
Jeon et al. 2013 Korea	Retro	ANSD SNHL	11, 4 to 8 years, 6 girls SNHL: 9	NR	Nucleus, AB	Uni	ANSD: 40.4 (8 to 80) SNHL: 29.4 (13 to 59)	Postoperative eABR[d]	CAP	eABR was not recorded in 6 out of 11 children with ANSD. Children with recorded eABR showed relatively good speech performance post-CI, while the nonresponse

										group demonstrated variable outcomes.
Jeong and Kim 2013 Korea	Retro	ANSD	15, 3.5 years, 5 girls	70	Nucleus	NR	72.8	Postoperative eABR (3 weeks post-CI)	CAP, IT-MAIS, open-set MWT	eABR results were not different in children with good and poor speech perception outcomes.
Jin et al. 2013 China	Retro	CND (IACS) Matched SNHL	NA	NA	NA	NA	NA	Intraoperative eABR	CAP, SIR	A higher threshold and lower dynamic range of eABR, and lower speech performance outcomes were identified in the IACS group compared to the control group. The CAP score and eABR grade were correlated.
Valero et al. 2012 Canada	Retro	ANSD with hypoplasia Matched SNHL	19, 10 girls	ANSD: 50.4 (12-155) SNHL: 51.24 (12-172.2)	Nucleus	ANSD: 17/2 SNHL: 17/2	At CI activation and every 3 months up to 24 months	Postoperative eABR	ESP, IT-MAIS, WIPI, GASP, MLNT, BKB word,s LNT phonemes	In children with hypoplasia, single eV waves were recorded in some children, but most responses were abnormal. eV was also significantly delayed compared with the control group. Speech performance, the

									, BKB phonemes	PROSPER score,[d] was poor in both the initial and the most recent assessment and did not improve over time.
Song et al. 2010 Korea	Retro	CND, 9 with aplasia	13, 4.3 (1-13) years,	NR	Nucleus, AB	NR	26.5 (12-68)	Intra- and postoperative eABR and eCAP at 1, 3, 6, 12, 18, and 24	CAP, IT-MAIS	The average IAC was 1.78 mm (0.75-2.57 mm). Post-CI CAP scores ranged from 0 to 4. eABR was good, variable, and absent in 4, 3, and 6 children, respectively, which corresponded with CAP scores 4, 4 or 2, and 2 or 0, respectively.
Gibson et al. 2009 Australia	Retro	SNHL	245	NR	Nucleus	NR	12 months for 245 children 24 months for 148 children	Intraoperative eABR	MSPS[e]	eABR waveforms were significantly different between those who scored 4≥ compared to lower scores in the Melbourne scale. After two years, the outcome showed greater differences.

Kim et al. 2008 USA	Retro	CVN abnormalities G1: Mondini G2: other CV abnormalities G3: Aplasia	G1: 11 G2: 20 G3: 8	12-159	Nucleus, AB, MedEl	All uni	36	Preoperative promontory eABR	GASP for words and sentences, NUCHIP, minimal pairs test	Children with lower preoperative eABR thresholds had better postoperative speech performance. Larger eV amplitude and shorter latency were associated with better speech performance. Open-set sentence recognition test was possible in 73% of group 1, 30% of group 2, and 38% of group 3.
Walton et al. 2008 Australia	Retro	A: Bilateral ANSD B: Bilateral ANSD with CND[f]	≤15 years A: 39, 14 girls B: 15, 7 girls	A: 40 B: 44	Nucleus	NR	12	Postoperative eABR, axial T2 MRI	MSPS	Children with CND showed worse speech perception scores (median score 1 vs. 4), higher rates of abnormal eABR (87% vs. 23%), and more associated inner ear abnormalities than children with ANSD without CND.

Nikolopoulos et al. 2000 UK	Pros	SNHL	N: 47 G1: 35 with clear eV G2: 12 without eABR	58	NR	NR	12, 24, and 36	Intraoperative eABR at the time of CI surgery	Iowa sentence test, CDT, CAP, SIR	Children with no preoperative eABR performed at levels comparable with children who had clear preoperative eABR.

AB: Advanced Bionics, ANSD: auditory neuropathy spectrum disorder, BKB: Bamford-Kowal-Bench sentence test, CAP: Categories of Auditory Performance, CDI: child development inventory; CDT: Connected Discourse Tracking, CI: cochlear implant, CVN: cochleovestibular nerve, DEAP: diagnostic evaluation of articulation and phonology, eABR: electric auditory brainstem response, ESP: early speech perception, G: group, GASP: Glendonald Auditory Screening Procedure, IACS: internal auditory canal stenosis, LNT: lexical neighborhood test, MLNT: Multi-syllable Lexical Neighborhood Test, MSPS: Melbourne speech perception score, NA: not accessible, NR: not reported, Pros: prospective, Retro: retrospective, SIR: Speech Intelligibility Rating, SNHL: sensorineural hearing loss, SP: speech perception.

[a] Categories of implant evoked eABR waveform scores: Score 3: ell (yes), eIII (yes), eV (yes); Score 2: eII (no), eII (yes), eV (yes); Score 1: eII (no), eIII (no), eV (yes); Score 0: eII (no), eIII (no), eV (no) (Lundin et al. 2016: Gibson et al. 2009, with modifications).

[b] The eV was considered present (positive eV) when two or more tested electrodes showed evoked waves meeting the following criteria: 1) reproducible responses with amplitude greater than 0.15 KV, 2) a current-dependent increase in amplitude, which suggests a neuronal response rather than a myogenic response, and 3) 3.8 to 5.0 milliseconds of the wave latency (Yamazaki et al., 2015).

[c] Growth referred to improvement in CAP and SIR test scores.

[d] The results of eABR were grouped into 3 categories: 1) good response: reproducible wave V responses at all apical, middle, and basal electrodes, with an eABR threshold of less than 1750 KA; 2) variable response: reproducible wave V responses measured only in limited electrodes and/or an eABR threshold of more than 1750 KA; 3) nonresponse: no identifiable wave V response in any of the electrodes.

[e] MSPS includes 7 categories, in which levels 5, 6, and 7 show that open-set recognition of speech has been achieved (Walton et al., 2008).

[f] Comorbidity: A 78% and B 67%, severe comorbidity: A 24% and B 47%, brain abnormality: A 56% and B 53%, Inner ear abnormality: A 8% and B 93%.

Table 3. Characteristics of studies on the prognostic value of MRI findings for CI outcomes

Study Country	Study design	Diagnosis	Participants	Age at CI (months)	Device	Uni/ Bi	Follow-up period (months)	Imaging	Outcome measures	Findings
Kari et al. 2022 USA	Retro	CVN abnormalities, 20 with AD	40, 7-78 months,18 girls	NR	CLs, HAs, Bimodal	18/2 20 HAs	NR	T2 MRI and CT scan	Aided hearing thresholds, SAT	IAC midpoint diameter and the number of nerves in the IAC were predictors of post-CI outcomes.
Han et al. 2019 Korea	Retro	Bilateral CND	25, 21.0 months, 12 girls	NR	Nucleus	NR	24	MRI	CAP, IT-MAIS	The area ratio of CN to FN at the CPA was correlated with CAP and IT-MAIS scores.
Gaurav and Rajguru 2019 India	Pros	SNHL with or without MRI abnormalities [a]	50, 5.06 years, 25 girls	NR	Nucleus, AB	NR	12	MRI	CAP, MAIS	MRI abnormalities observed in 15 children were associated with lower post-CI outcomes.
Chung et al. 2018 Korea	Retro	CND	56 G1: 17, CNC<1.44 mm G2: 14 CNC between 1.4-2 mm G3: 25 CNC>2mm	G1: 27.92 G2; 29.32 G3: 33.43	NR	NR	6, 12, 24, and 36	MRI in the axial plane	CAP, open-set speech tests, picture vocabulary test	Groups 1 and 2 with smaller CNC diameters had poor post-CI outcomes, and group 3 with normal CNC diameters showed good CI outcomes.[b]

Birman et al. 2016 Australia	Retro	CND G1: aplasia 64% G2: hypoplasia 25% G3: normal CN 11% 54% with ADs	50, 0-16 years, 24 girls	Median 25	NR	29/21	12	MRI	CAP	CI outcomes were significantly affected by aplasia/hypoplasia and developmental delay. CAP scores were obtained between 5 and 7 for 47% and 89% of children with aplasia and hypoplasia, respectively. The main mode of communication was significantly influenced by the presence of developmental delay.
Chao et al. 2016 China	Retro	Bilateral CND Matched SNHL No AD/C	CND: 10, 6 girls SNHL: 10, 6 girls	CND: 4.45 (1.5-7.4) year SNHL: 4.0 (1.3-6.5) year	Nucleus	All uni	12	T2 MRI in the axial plane and CT scan	CAP, SIR	Poor outcomes in children with CND compared to children with SNHL. No association was identified between CN and CNC diameters and CI outcomes in CND. Overall, better results were obtained in children with CN>FN.
Jeong et al. 2015 Korea	Retro	CVN malformation A:16 B: 31 C: 6 D= 6[c] No narrow	59, 5.8 years, 27 girls	A: 5.82 B: 6.58 C: 3.07 D: 5.32	Nucleus	NR	36 or more	TBCT, MRI	Open-set MWT	Better post-CI speech perception scores were reported in CN malformation types A and B compared to types C and D. The test scores did not differ between types A and B and those without CN malformation.

		CNC with ADs Matched SNHL								
Jeong and Kim 2013 Korea	Retro	ANSD with CND	15, 3.5 years, 5 girls	70	Nucleus	NR	72.8	MRI and CT scan	CAP, IT-MAIS, open-set MWT	The normal size of CNC and CN was correlated with excellent speech perception abilities after CI. A narrow or obliterated CNC and a deficient CN were associated with poor speech perception abilities.
Yamazaki et al. 2015 Japan	Retro	CND, 4 with AD	19	2.67 (11.5)	Nucleus	5/14	24	T2 MRI in the axial plane and CT scan	Pre/posto perative CAP	Poor speech performance was found in children with FN>CN.
Valero et al. 2012 Canada	Retro	ANSD with hypoplasia Matched SNHL	19, 10 girls	ANSD: 50.4 (12 to 155) SNHL: 51.24 (12 to 172.2)	Nucleus	ANSD: 17/2 SNHL: 17/2	At CI activation and every 3 months up to 24 months	MRI and CT scan	ESP, IT-MAIS, WIPI, GASP, MLNT, BKB words, LNT phonemes, BKB phonemes	Speech performance, the PROSPER score,[d] was poor in both the initial and the most recent assessment and did not improve over time.

Teagle et al. 2010 USA	Retro	ANSD with medical comorbidities, 42% with prematurity	52, 7.3 years, 19 girls	47, 12-213	Nucleus, AB	2/50	41 (6-118)	MRI and CT scan	ESP, PBK, MLNT, LNT, IT-MAIS	38% had abnormal findings on preoperative MRI of the brain and inner ear. 50% demonstrated open-set speech perception abilities, and nearly 30% were unable to complete the test because of low CI experience or developmental delays. No child with CND achieved open-set speech perception abilities. In a subgroup of children with the results of MRI and PBK tests, good open-set speech perception skills were associated with normal MRI results.

AB: Advanced Bionics, AD/C: additional disabilities/comorbidities, ANC: auditory nerve canal, ANSD: auditory neuropathy spectrum disorder, BKB: Bamford-Kowal-Bench sentence test, CAP: Categories of Auditory Performance, CDI: child development inventory, CI: cochlear implant, CN: cochlear nerve, CNC: Consonant-Nucleus-Consonant, CPA: cerebellopontine angle, CVN: cochleovestibular nerve, ESP: early speech perception, FN: facial nerve, GASP: Glendonald Auditory Screening Procedure, HINT: Hearing in Noise Test, IAC: internal auditory canal, LNT: lexical neighborhood test, MLNT: Multi-syllable Lexical Neighborhood Test, NR: not reported, Pros: prospective, PROSPER: Pediatric Ranked Order Speech Perception, Retro: retrospective, SAT: speech awareness threshold, SIR: Speech Intelligibility Rating, SNHL: sensorineural hearing loss, SP: speech perception, TBCT: temporal bone computed tomography, VCN: vestibulocochlear nerve, WIPI: Word Intelligibility by Picture Identification.

[a] Demyelination of the brain white matter (n = 9), Mondini's dysplasia (n = 1), communicating hydrocephalus (n = 1), asymmetrical cochlear size (n = 1), and features of mastoiditis (n = 3).

[b] Overall, the correlation between CAP score and CNC diameter at 24 and 36 months was 0.377 and 0.395; the correlation between open-set word discrimination score and CNC diameter at 24 months was 0.533, and the correlation between CNC diameter and picture vocabulary test score was 0.342.

[c] Four subtypes of cochleovestibular nerve (CVN) malformation were introduced based on the cochlea and modiolus morphology: normal cochlea and normal modiolus (type A, n = 16), malformed cochlea and partial modiolus (type B, n = 31), malformed cochlea and no modiolus (type C, n = 6), and no cochlea and no modiolus (type D, n = 6).

Table 4. Quality assessment of the included papers using the Crowe Critical Appraisal Tool (CCAT)

Study	Preliminaries	Introduction	Design	Sampling	Data collection	Ethics	Results	Discussion	Total/40	Total (%)[a]
Kari et al. 2022	5	5	3	3	4	4	5	4	33/40	82.5
Han et al. 2019	4	4	3	3	4	5	4	4	31/40	77.5
Chung et al. 2018	4	4	3	3	4	4	3	3	28/40	70.0
Motasaddi Zarandy et al. 2018	3	3	3	3	3	3	2	2	22/40	55.0
Attias et al. 2017	5	4	4	4	4	4	4	3	32/40	80.0
Birman et al. 2016	5	4	4	4	4	3	4	3	31/40	77.5
Gaurav and Rajguru 2016	4	4	3	3	3	3	2	2	24/40	60.0
Chao et al. 2016	4	4	3	3	3	3	3	3	26/40	65.0
Jeong et al. 2015	4	5	4	4	3	3	4	4	31/40	77.5
Wang et al. 2015	4	5	3	3	3	3	4	4	29/40	72.5
Yamazaki et al. 2015	4	4	3	3	4	3	3	4	28/40	70.0
Jeon et al. 2013	4	4	3	3	2	2	3	4	25/40	62.5

Jeong and Kim 2013	4	4	3	3	2	2	4	3	25/40	62.5
Jin et al. 2013	4	4	3	3	2	2	3	3	27/30	67.5
Valero et al. 2012	5	4	4	4	4	3	4	5	33/40	82.5
Fulmer et al. 2011	4	4	3	2	3	3	3	3	25/40	62.5
Buchman et al. 2011	5	4	4	5	4	2	4	4	32/40	80.0
Cosetti et al. 2010	3	4	3	4	3	0	4	2	23/40	57.5
Song et al. 2010	4	4	3	3	3	0	4	3	24/40	60.0
Teagle et al. 2010	5	5	4	4	4	2	4	4	32/40	80.0
Gibson et al. 2009	2	4	3	4	3	0	2	2	20/20	50.0
Kim et al. 2008	4	4	4	3	3	2	4	3	27.40	67.5
Walton et al. 2008	4	4	4	3	4	0	4	4	27/40	67.5
Guedes et al. 2007	3	4	4	4	3	3	3	4	28/40	70.0
Nikolopoulos et al. 2000	3	4	4	3	3	0	3	2	22/40	55.0

[a] For each paper, eight aspects of the CCAT were evaluated using a 6-point rating scale (from zero to five), and the total score was 40 (Crowe et al., 2012).

Table 5. Using the GRADE tool for narrative synthesis and rating the certainty of evidence (Murad et al., 2017)

Outcome **Effect** **Total number of participants**	**GRADE domains**	**Judgment**	**Certainty in the evidence***
Outcome 1: Prognostic value of eCAP **Effect: Predicting CI outcomes** **Total number of participants: 335**	Methodological limitations	Judgment was made based on key criteria for observational studies: failure to develop and apply appropriate eligibility criteria, flawed measurement of exposure and outcome, failure to adequately control confounding, and incomplete or inadequately short follow-up (Schünemann et al., 2013).	Low ⨁⨁OO
	Indirectness	Patients, interventions, and comparator groups (control or baseline comparison) provided most of the direct evidence for the research question. Different speech-language tests and/or questionnaires were used to access post-CI outcomes. Evidence was judged to have no serious indirectness but noted some variability in the intervention (the eCAP test) and outcome measures.	High ⨁⨁⨁⨁
	Imprecision	The sample size of the 10 included studies ranged from 10 (Fulmer et al., 2011; Motasaddi Zarandy et al., 2018) to 97 (Cosetti et al., 2010); seven were below 25, and three were between 52 and 97.	Low ⨁⨁OO
	Inconsistency	The direction and/or magnitude of the prognostic value of eCAP varied across studies showing relevance or no relevance for CI outcomes.	Low ⨁⨁OO
	Publication bias	Publication bias was not strongly suspected because all studies had been published in peer-reviewed journals, and the systematic search for studies was comprehensive.	High ⨁⨁⨁⨁
Summary of certainty in evidence for the first outcome			Low†‡ᅀ ⨁⨁OO

Outcome 2: Prognostic value of eABR **Effect: Predicting CI outcomes** **Total number of participants: 502**	Methodological limitations	Judgment was made based on key criteria for observational studies mentioned in the first outcome (Schünemann et al., 2013).	Low ⊕⊕OO
	Indirectness	In most studies, the patients, interventions, and comparators (the control group or baseline) provided direct evidence. Evidence was judged to have no serious indirectness but noted some variability in the intervention (the eABR test) and outcome measures.	High ⊕⊕⊕⊕
	Imprecision	The sample size of 11 included studies varied between 11 (Jeon et al., 2013) and 245 (Gibson et al., 2009); six were below 25, four were between 39 and 245, and one was not reported.	Low ⊕⊕OO
	Inconsistency	The direction and/or magnitude of the prognostic value of eABR for CI outcomes had little variability.	High ⊕⊕⊕⊕
	Publication bias	Publication bias was not strongly suspected because all studies had been published in peer-reviewed journals, and the systematic search for studies was comprehensive.	High ⊕⊕⊕⊕
Summary of certainty in evidence for the second outcome			Low †‡ ⊕⊕OO
Outcome 3: Prognostic value of MRI **Effect: Predicting CI outcomes**	Methodological limitations	Judgment was made based on key criteria for observational studies mentioned for the first outcome (Schünemann et al., 2013).	Low ⊕⊕OO
	Indirectness	The research questions were mostly answered using patients, interventions, and comparators (the control group or baseline). There were no serious indirect effects, however, some variability was noted in the intervention (MRI) and outcome measurements.	High ⊕⊕⊕⊕

Total number of participants: 395	Imprecision	The number of participants in 10 included studies varied between 10 (Chao et al., 2016) and 59 (Jeong and Kim, 2015); 5 studies were ≤ 25, and 5 studies were between 50 and 59.	Moderate certainty ⨁⨁⨁O
	Inconsistency	The direction and/or magnitude of the prognostic value of MRI for CI outcomes had little variability.	High ⨁⨁⨁⨁
	Publication bias	Publication bias was not strongly suspected because all studies had been published in peer-reviewed journals, and the systematic search for studies was comprehensive.	High ⨁⨁⨁⨁
Summary of certainty in evidence for the third outcome			Low † ⨁⨁OO

CI: cochlear implant, eABR: electric auditory brainstem response, eCAP: electric compound action potential, GRADE: the Grading of Recommendations, Assessment, Development, and Evaluation, NRT: neural response telemetry.

*Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⨁⨁⨁⨁, moderate certainty ⨁⨁⨁O, low certainty ⨁⨁OO, and very low certainty ⨁OOO (Murad et al. 2019).

†Serious methodological limitations (failure to develop and apply appropriate eligibility criteria, diversity in outcome measures, and failure to adequately control confounding).

‡Serious imprecision (small sample sizes in the majority of studies).

⅄Serious inconsistency (no relevance of eCAP findings to CI outcomes).

Chapter 4

Title: An Umbrella Review of Cochlear Implant Outcomes in Children with Auditory Neuropathy

Short Title: Cochlear Implant Outcomes in ANSD

Authors: Zahra Jafari[1], Elizabeth M. Fitzpatrick[1,2], David R. Schramm[3,4], Isabelle Rouillon[5], Amineh Koravand[1]

[1]Audiology and Speech-Language Pathology Program, University of Ottawa, Ottawa, Ontario, Canada.

[2]Child Hearing Laboratory, CHEO Research Institute, Ottawa, Ontario, Canada.

[3]Department of Otolaryngology-Head and Neck Surgery, University of Ottawa, Ottawa, Ontario, Canada.

[4]Department of Otolaryngology-Head and Neck Surgery, The Ottawa Hospital, Ottawa, Ontario, Canada.

[5]Department of Pediatric Otolaryngology, AP-HP, Hôpital Necker-Enfants Malades, Paris, France.

Corresponding author: Amineh Koravand

Jafari Z, Fitzpatrick EM, Schramm DR, Rouillon I, Koravand A. An Umbrella Review of Cochlear Implant Outcomes in Children with Auditory Neuropathy. *Journal of Speech, Language, and Hearing Research.* Published. Aug 2023.

Abstract

Purpose: The objective of this overview of systematic reviews (SRs) (umbrella review) was to systematically summarize and critically appraise current evidence of cochlear implant (CI) outcomes in children with auditory neuropathy spectrum disorder (ANSD).

Method: The present study was guided by the PRISMA 2020 statement. The methodological quality and the risk of bias in the included SRs were assessed using the AMSTAR-2 checklist and the ROBIS tool, respectively.

Results: According to eight included SRs, children with ANSD achieve CI outcomes (speech perception performance) similar to their peers with sensorineural hearing loss (SNHL). In children with postsynaptic ANSD (cochlear nerve deficiency CND), cochlear nerve hypoplasia is associated with better speech recognition outcomes compared to cochlear nerve aplasia, especially in the absence of additional disabilities. Except for one study, the overall quality of the included SRs was critically low; and except for three studies, evidence of a high risk of bias was identified in other included SRs.

Conclusions: Current evidence supports CI benefits for children with ANSD. To improve the quality of evidence, well-designed, prospective studies with appropriate sample sizes, using valid outcome measures, clarifying matching criteria, and taking into account the role of confounding factors are essential.

Keywords: Auditory neuropathy spectrum disorder; Cochlear nerve deficiency; Cochlear implant; Speech performance; Outcome; Systematic review

Introduction

Auditory neuropathy spectrum disorder (ANSD) is characterized by the involvement of the peripheral auditory system leading to impaired temporal coding of acoustic signals and impaired auditory perception (Santarelli et al., 2021). Based on the anatomic locus of dysfunction and audiologic and electrophysiologic findings, ANSD is broadly classified into "pre-synaptic and postsynaptic disorders". In presynaptic ANSD (or auditory synaptopathy, auditory dyssynchrony), predominately resulting from genetic etiologies such as otoferlin and DIAPH 3 mutations, the lesion site is the inner hair cells or ribbon synapses (Rance and Starr, 2015). In postsynaptic ANSD, dysfunction can occur at multiple sites along the auditory nerve pathway, including unmyelinated auditory nerve dendrites or auditory ganglion cells and their myelinated axons and dendrites (Rance and Starr, 2015; Shearer and Hansen, 2019). While demyelination slows conduction velocity causing dyssynchrony (i.e., deficiency in neural synchrony), axonal degeneration results in reduced auditory input to the brainstem (i.e., deficiency in neural transmission) (Hall, 2015; Rance and Starr, 2015). The involvement of each of these anatomic sites or multisite involvement can lead to deficits in neural synchrony and/or neural transmission and severely affect auditory temporal processing (He et al., 2015; Rance et al., 2004; Santarelli et al., 2021).

ANSD has a heterogeneous clinical profile. Various factors or diseases may contribute to ANSD, such as perinatal and neonatal factors (e.g., hypoxia, hyperbilirubinemia, and ototoxic drug exposure), genetic and hereditary etiologies, demyelinating diseases, and neurodegenerative disorders (e.g., Friedreich ataxia) (Chaudhry et al., 2020; Rance and Starr, 2015). In approximately 27.0% to 33.0% of children, ANSD results from cochlear nerve deficiency (CND) (Hall, 2015), and 30,0% of children with ANSD present with at least one additional disability other than hearing loss (Berlin et al., 2010; Ching et al., 2013a). CND is characterized by a very abnormal auditory

nerve structure, including a small (hypoplastic) or absent (aplastic) cochlear nerve as revealed by high-resolution MRI (Hall, 2015; Roche et al., 2010). MRI in the axial and sagittal planes allows for precisely differentiating cochlear nerve aplasia and hypoplasia. As the candidacy criteria for cochlear implantation (CI) have been expanded, more patients with CND undergo CIs with widely varying outcomes (Peng et al., 2017).

Many children with ANSD and permanent hearing loss are candidates for CI operation, and they can benefit from early implantation like their peers with sensorineural hearing loss (SNHL) (Breneman et al., 2012; Shearer and Hansen, 2019). In addition, for families who desire spoken language as the primary mode of communication, CIs are a feasible option when children show poor progress with properly fitted hearing aids (HAs) (JCIH, 2019). Like children with SNHL, better outcomes for ANSD are associated with receiving CIs before three years of age (Ching et al., 2013a; Ching et al., 2013b; Niparko et al., 2010). While most children with SNHL can achieve typical rates of speech, language, and academic development (Leigh et al., 2011), the CI outcomes of children with ANSD are widely diverse (Bo et al., 2022; Cupples et al., 2018; Myers and Nicholson, 2021; Peng et al., 2017; Rajput et al., 2019; Rance and Starr, 2015; Vesseur et al., 2018). The majority of children with ANSD may attain speech understanding, language development, and communication outcomes equivalent to their peers with SNHL (Madden et al., 2002; Mason et al., 2003; Rance and Barker, 2009; Santarelli et al., 2015; Shallop, 2002; Teagle et al., 2010; Zeng and Liu, 2006). However, a subgroup of children with ANSD (almost 25.0%) show limited benefits from CIs and cannot develop functionally useful auditory communication skills (Gibson and Sanli, 2007; Roush et al., 2011; Teagle et al., 2010). In these children with postsynaptic ANSD (i.e., CND), post-implantation outcomes are directly associated with the lesion site(s) (Shearer and Hansen, 2019). Therefore, to early identify children with CND and assist in

decision-making about appropriate auditory interventions, MRI and genetic findings, and the results of auditory behavioral and electrophysiological assessments are essential (Rance and Starr, 2015).

During the past decade, several systematic reviews (SRs) were published on CI outcomes in children with pre-synaptic and/or postsynaptic ANSD (Bo et al., 2022; Humphriss et al., 2013; Myers and Nicholson, 2021; Peng et al., 2017; Rance and Starr, 2015; Vesseur et al., 2018). Current evidence demonstrates a range of CI outcomes in children with ANSD from no significant difference relative to peers with SNHL (Bo et al., 2022) to poor auditory performance in a fraction of patients with postsynaptic involvement or evidence of CND (Gibson and Sanli, 2007; Roush et al., 2011; Teagle et al., 2010). With a substantial increase in research publications, evidence synthesis has become an instrumental tool to identify and concisely summarize knowledge on specific topics (Cant et al., 2022). Umbrella reviews (overview of reviews or summary of SRs) were developed in response to the increased number of SRs and meta-analyses in health-related literature. Umbrella reviews save valuable research resources by avoiding systematic searches from scratch. This type of review consists of explicit and systematic methods to search for, identify, and synthesize SRs on a similar topic (Pollock et al., 2022), and offers clinicians, policy-makers, researchers, educators, and interested readers a synopsis of SRs on a frequent question (Cant et al., 2022). The objective of this umbrella review was to systematically summarize and critically appraise current SRs of CI outcomes in children with ANSD including those with evidence of CND, and to discuss directions for future research.

Methods

This review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021).

PICOS Framework

Formulating a research question is a teamwork process aimed at collaborating with others involved in the study to shape the primary purpose of the work for the desired outcome. Several frameworks are available to develop a well-formulated question for SRs (Methley et al., 2014). In evidence-based research, the PICOS tool focused on **P**opulation, **I**ntervention, **C**omparison, **O**utcomes, and **S**tudy design is a common tool to identify components of clinical evidence for systematic reviews (Higgins and Green, 2013). Appendix A presents the PICOS framework established for the present overview of SRs.

Search Strategy

Relevant SRs were identified using a systematic search strategy across the following five databases: ProQuest, PubMed, Scopus, Ovid, and the Cochrane Database of Systematic Reviews. Appendix B presents the search strategy established for this review. The SR protocol was uploaded to PROSPERO (i.e., an international database of prospectively registered SRs with health-related outcomes, registration number: CRD42023389156).

Study Selection

All retrieved articles were imported into EndNote X7 software and duplicate publications were excluded (Thomson Reuters, Philadelphia, Pennsylvania, USA, version X7). The final articles were assessed through a three-stage process: title screening, abstract screening, and full-text screening. All SRs reporting post-implantation auditory, speech, and/or language outcomes in children with ANSD, with or without statistical methods (i.e., meta-analyses), were considered. Articles that did not meet the inclusion criteria were excluded at each stage. In cases of uncertainty about title screening, first, the abstracts and then the full texts were screened. Pairs of reviewers

(ZJ and AK) independently screened the titles, abstracts, and full texts of articles. Any potential disagreements were resolved by consensus. Overall, there was complete agreement between the reviewers on the included SRs.

The following data extracted from SRs were included in the review: authors, publication year, databases searched, number of primary studies reviewed, population (i.e., ANSD, CND, SNHL), the total number of participants in each SR, age at CI activation, duration of CI use, and reported outcomes. It was not necessary to contact the authors of the included SRs for further information since all relevant data were available in the selected SRs.

Quality Assessment

The methodological quality of the included SRs was assessed using the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) checklist (Shea et al., 2017) (Appendix VI). The revised checklist consists of 16 criteria that enable a more detailed assessment of SRs including randomized or non-randomized studies of healthcare interventions, or both. Seven out of 16 items in AMSTAR-2 are considered critical domains, including items two (a statement showing that the review methods were established prior to the conduct of the review), four (using a comprehensive literature search strategy), seven (providing a list of excluded studies without justifying the exclusions), nine (using a satisfactory technique for assessing the risk of bias in primary studies), 11 (reporting meta-analysis with an appropriate method), 13 (referring to the risk of bias in individual studies when discussing the results of the review), and 15 (stating that the risk of bias might have affected the results of the review). AMSTAR-2 proposes a four-level rating scheme consisting of high (no or one non-critical weakness), moderate (more than one non-critical weakness), low (one critical flaw with or without non-critical weaknesses), and critically low (CL: more than one critical flaw with or without non-critical weaknesses) for appraisers to rate the

overall confidence in the results of an SR. In addition, the evaluation of the domains entails three options: “yes”, “partial yes” and “no”, which are assigned points of 1, 0.5, and 0.0, respectively (He et al., 2019). Two reviewers (ZJ and AK) independently assessed the quality of the SRs, and disagreements were resolved by consensus. Overall, the reviewers were in complete agreement regarding the quality of the included SRs.

Risk of Bias Assessment

The risk of bias in the included SRs was assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool (Whiting et al., 2016) (Appendix VII). ROBIS consists of three phases: assessing the relevance, identifying concerns about the review process, and judging the risk of bias. Phase one includes one item and evaluates whether participants, exposures, comparators, and outcomes match the target question. The answers are “yes,” “no,” “partial,” and “uncertain”. Phase two involves four domains: (1) study eligibility criteria; (2) identification and selection of studies; (3) data collection and study appraisal; and (4) synthesis and findings. Phase two signaling questions are answered as “yes,” “probably yes,” “probably no,” “no” and “no information”. Based on the answer to each indicator question, the bias associated with each domain is then judged as “low,” “high,” or “unclear.” Phase three considers whether the SR as a whole is at risk of bias. Several questions were examined in this phase: (1) Did the interpretation of findings address all the concerns identified in domains one through four? (2) Was the relevance of the identified studies appropriately considered in the review's research question? and (3) Did the reviewers avoid emphasizing only the statistical significance of the results? The answers to these signaling questions are similar to those in phase two. Based on the answers to the questions in phase three, the overall risk of bias in SRs is rated as “low,” “high,” or “unclear.” In this overview of SRs, two

reviewers independently evaluated the risk of bias in each included SR, and disagreements were resolved through discussion. Quality assessment was performed by one reviewer (ZJ) and then verified by another (AK). Overall, there was complete agreement in assessing the risk of bias between the reviewers.

Results

Results of the Literature Search

The database search yielded 446 publications, including 288 duplicate records that were removed (Figure 1). After screening titles, 148 more records were eliminated, including non-review articles (n = 108), non-SRs (n = 38), and out-of-scope SRs (n = 2) (Boisvert et al., 2020; Merkus et al., 2014). Out-of-scope SRs referred to publications that did not meet the inclusion criteria. This initial screening resulted in a set of 12 papers. Subsequently, during the screening of abstracts, four more SRs (Amin et al., 2019; Rødvik et al., 2018; Roush et al., 2011; Shafiro et al., 2021), not relevant to the topic of this review, were eliminated leaving eight studies for this review. In addition, the reference lists for the selected publications were hand-searched for additional related publications. No further related articles were identified.

Characteristics of the Included SRs

Table 1 summarizes the characteristics of the selected SRs in this review. The number of primary studies reviewed in the SRs ranged from four (Myers and Nicholson, 2021) to 27 (Humphriss et al., 2013). There were eight studies included in this review, three of which focused on children with ANSD and included children with SNHL as the control group (i.e., children with SNHL) (Bo et al., 2022; Fernandes et al., 2015; Humphriss et al., 2013), two were on children with

ANSD without a control group (Chaudhry et al., 2020; Rajavenkat et al., 2021), one was on children with ANSD including two studies with a control group (children with SNHL) and two pre/post interventions comparing age at CIs before and after 24 months of age (Myers and Nicholson, 2021), and two were on patients with CND without a control group (Peng et al., 2017; Vesseur et al., 2018). Except for one study that consisted of case reports or case series of both children and adults (Chaudhry et al., 2020), all the SRs had reported CI outcomes in children only. The quality of the included primary studies was not assessed in three SRs (Fernandes et al., 2015; Peng et al., 2017; Vesseur et al., 2018). The SRs were different in terms of the outcome measures and the study design of the included primary studies (Table 1).

Methodological Quality of Evidence

Table 2 presents the AMSTAR-2 assessment results. Based on the proposed AMSTAR-2 rating scheme, there was low confidence in the results of one review (Bo et al., 2022), and CL confidence in the rest of the SRs. In terms of critical factors in AMSTAR-2 that affected the quality of evidence, items two, four, seven, nine, 11, 13, and 15 were deficient in three (Fernandes et al., 2015; Peng et al., 2017; Vesseur et al., 2018), two (Fernandes et al., 2015; Peng et al., 2017), seven (Bo et al., 2022; Chaudhry et al., 2020; Fernandes et al., 2015; Humphriss et al., 2013; Myers and Nicholson, 2021; Peng et al., 2017; Vesseur et al., 2018), four (Fernandes et al., 2015; Peng et al., 2017; Rajavenkat et al., 2021; Vesseur et al., 2018), seven (Chaudhry et al., 2020; Fernandes et al., 2015; Humphriss et al., 2013; Myers and Nicholson, 2021; Peng et al., 2017; Rajavenkat et al., 2021; Vesseur et al., 2018), four (Fernandes et al., 2015; Peng et al., 2017; Rajavenkat et al., 2021; Vesseur et al., 2018), and six (Fernandes et al., 2015; Humphriss et al., 2013; Myers and Nicholson, 2021; Peng et al., 2017; Rajavenkat et al., 2021; Vesseur et al., 2018) SRs, respectively.

Risk of Bias in the Included SRs

The ROBIS tool was used to assess the risk of bias in the included SRs (Whiting et al., 2016). This tool consists of a 5-choice rating scale (yes, probably yes, probably no, no, and no information), and phases two and three are generally rated as low, high, or unclear. Table 3 summarizes the results of ROBIS for the included SRs in four domains of phase two (1. study eligibility criteria, 2. identification and selection of studies, 3. data collection and study appraisal, and 4. synthesis and findings) and phase three (overall risk of bias in the SR). In domain one of phase two, three studies were scored with a high risk of bias (Myers and Nicholson, 2021; Rajavenkat et al., 2021; Vesseur et al., 2018). In domain two of phase two, five studies had indications of a high risk of bias (Fernandes et al., 2015; Myers and Nicholson, 2021; Peng et al., 2017; Rajavenkat et al., 2021; Vesseur et al., 2018). In domain three of phase two, four SRs were scored with a high risk of bias (Fernandes et al., 2015; Peng et al., 2017; Rajavenkat et al., 2021; Vesseur et al., 2018). In domain four of phase two, three SRs had a high risk of bias (Fernandes et al., 2015; Rajavenkat et al., 2021; Vesseur et al., 2018). In phase three, four studies had a high risk of bias (Fernandes et al., 2015; Peng et al., 2017; Rajavenkat et al., 2021; Vesseur et al., 2018). Three SRs had a low risk of bias in both phases two and three (Bo et al., 2022; Chaudhry et al., 2020; Humphriss et al., 2013), and two SRs had a high risk of bias in both phases two and three (Rajavenkat et al., 2021; Vesseur et al., 2018).

CI Outcomes in ANSD

Six out of eight SRs included in this review consisted of observational studies (i.e., prospective, retrospective, case-control, case series, and case reports) on children with ANSD (Table 1). Post-implantation outcomes were assessed using various speech and language assessments and relevant standard questionnaires. Four out of six SRs on children with ANSD had

peers with SNHL as the control group (Bo et al., 2022; Fernandes et al., 2015; Humphriss et al., 2013; Myers and Nicholson, 2021), and two other studies had no comparison groups (Chaudhry et al., 2020; Rajavenkat et al., 2021).

CI Outcomes in CND

Two out of eight SRs included in this umbrella review were performed on case series and case reports of children with aplasia and/or hypoplasia (Table 1). In both SRs, because of the diversity of primary studies (case reports and case series) in outcome measures, post-implantation performance was defined based on the "level of auditory performance" classification. According to this scale, CI outcomes are classified into four levels: level 1, non-stimulation or minimal detection; level 2, improved detection with parents' perceived benefit; level 3, closed-set speech perception; and level 4, open-set speech perception (Young et al., 2012).

Discussion

Our overview of existing SRs indicates that 1) despite heterogeneity within studies and patients, children with ANSD can achieve CI outcomes comparable to their peers with SNHL. 2) In children with CND, the presence of a cochlear nerve (hypoplasia vs. aplasia) on MRI and the absence of additional disabilities and/or medical comorbidities (ADs/MCs) are associated with better hearing and speech recognition outcomes compared to aplasia along with ADs/MCs. In the quality assessment, except for one study (Bo et al., 2022) with low quality, the overall quality of the included SRs was assessed as CL. In addition, in assessing the risk of bias with the ROBIS tool, except for three studies (Bo et al., 2022; Chaudhry et al., 2020; Humphriss et al., 2013), there were one or more indications of a high risk of bias in the SRs. In the following paragraphs, the main findings of the present review are discussed taking into account the risk of bias in the included SRs and the quality of evidence.

CI Outcomes in Children with ANSD

According to existing evidence, in children with ANSD, CI outcomes vary widely ranging from similar results with children using HAs, better outcomes compared to those using HAs, and poor CI outcomes in children with postsynaptic ANSD (Bo et al., 2022; Chaudhry et al., 2020; Humphriss et al., 2013). In a recent SR and meta-analysis by Bo et al. (2022), the post-CI outcomes of children with ANSD were compared with peers with SNHL who received CIs under 16 years. In this SR, 15 observational studies met the selection criteria and were considered for data analysis (Bo et al., 2022). In the meta-analysis, the pooled data showed no significant difference between the two groups in speech recognition scores, categories of auditory performance (CAP) scores, speech intelligibility rating (SIR) scores, and open-set speech perception test scores. In addition, no publication bias was identified among the included studies. The authors concluded that substantial heterogeneity within studies in CI outcomes might result from a combination of factors (e.g., the lesion site, age at implantation, cognitive and socioeconomic status, and comorbid conditions), especially the lesion site (Bo et al., 2022; Riggs et al., 2017). In patients with ANSD, the lesion site along the auditory pathway has a prognostic significance, in which patients with presynaptic ANSD or distal auditory nerve lesions (e.g., the involvement of inner hair cells [IHCs] or cochlear synapses) can achieve optimal outcomes compared to children with postsynaptic involvement (Chaudhry et al., 2020; Shearer and Hansen, 2019). The Bo et al. (2021) study was the only included SR with a low risk of bias in methodological quality assessment and had no risk of bias with the ROBIS tool. However, the authors emphasized that the findings should be interpreted with caution because of the small sample size of most included studies (between 8 and 35 children in the ANSD group), which might contribute to overestimating intervention outcomes.

The objective of the SR by Myers and Nicholson (2021) was to evaluate the evidence regarding the efficacy of CIs in children with ANSD, who received CIs below three years of age. In two (Alzhrani et al., 2019; Ching et al., 2013a) out of four studies included in this SR, the CI outcomes of children with ANSD were compared to peers with SNHL. In both studies, no significant difference was identified between the two groups. In the other two studies (Daneshi et al., 2018; Liu et al., 2014), to compare children implanted before and after 24 months of age, the CAP and SIR test scores were used as outcome measures. In the Liu et al. (2014) study, children who were implanted below 24 months of age achieved superior speech performance outcomes relative to older children implanted after 24 months of age. In the Daneshi et al. (2018) study, the CAP scores were significantly improved in children implanted before relative to after 24 months of age, but the two groups did not significantly differ in the SIR score. Overall, the results of this SR were in support of CI as an effective intervention for improving auditory, speech, and language outcomes in children with ANSD. Low sample sizes and no control over ADs/MCs were the major limitations of the four primary studies included in this SR. In addition, the SR was limited to two databases for systematic search and had a narrow time frame (between 2009 and 2019). In the present overview, the overall quality of this SR was also assessed as CL, and the study had two indications of a high risk of bias in the ROBIS tool.

In 2 other SRs, the CI outcomes of children with ANSD were compared to their peers with SNHL (Fernandes et al., 2015; Humphriss et al., 2013). In the Humphriss et al. (2013) study, several serious methodological limitations were reported in the quality assessment of primary studies. In the Fernandes et al. (2015) study, no tool was used for quality assessment. In both SRs, children with ANSD had similar post-implantation outcomes to peers with SNHL. In the present overview, the quality of both SRs was assessed as CL. In assessing the risk of bias, the study by

Humphriss et al. (2013) had no risk of bias, and the SR by Fernandes et al. (2015) showed indications of risk of bias in all areas of the ROBIS tool, except for the study eligibility criteria (Table 3). Both SRs suffered from similar shortcomings reported by Bo et al. (2022), including the low quality of evidence and small sample sizes in the included primary studies. In addition, the authors did not discuss the impact of ADs/MCs on outcomes.

The study by Chaudhry et al. (2020) was an SR of 14 case reports and case series (including three studies with a control group with SNHL) reporting pre-CI and post-CI outcomes for children and adults with postsynaptic ANSD. Of 14 studies (consisting of 25 patients in total, one to eight patients per study), four reported patients with Charcot-Marie-Tooth disease (CMT), three with Brown-Vialetto-Van-Laere syndrome (BVVL), two with Friedreich Ataxia (FRDA), two with Syndromic dominant optic atrophy (DOA+), two with cerebellar ataxia - areflexia - pes cavus - optic atrophy - SNHL (CAPOS) syndrome, and 1 with deafness-dystonia-optic neuropathy (DDON) syndrome. Using the Oxford Centre for Evidence-Based Medicine (OCEBM) checklist, the studies were graded with low quality often because of the study design (i.e., case reports or case series) and lack of sufficient information regarding outcome measures and/or findings. In addition, all included primary studies had indications of a high risk of bias assessed by the Brazzelli Risk of Bias Assessment (Brazzelli et al., 2015). Despite the diversity of primary studies in outcome measures (using a variety of validated or non-validated tests of auditory, speech, and language performance) and results, overall findings were suggestive of favorable post-CI outcomes, ranging from modest to statistically significant benefit in 22 out of 25 patients included in the SR. However, the authors concluded that because of substantial methodological limitations (e.g., the low quality of the included studies, the potential role of confounding factors on the outcomes, diversity in outcome measures, and high heterogeneity in follow-up periods between

two and 12 months), the findings could not be generalized to all patients with postsynaptic ANSD. In the present overview, this SR had no indication of the risk of bias in the ROBIS tool, but it was rated CL in assessing the level of evidence.

Recently Rajavenkat et al. (2021) summarized the CI outcomes of 291 children with ANSD from nine case series, retrospective, and prospective studies published between 2012 and 2018. Although some of the included studies had a control group with SNHL, the study was unclear regarding the existence of a control group in some included studies, and "no comparison group" was reported in the selection criteria (i.e., PICOS). Moreover, irrespective of the study design of primary studies, the authors reported a low risk of bias for all primary studies assessed by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) (Whiting et al., 2011), and no additional information was provided regarding the details of the quality assessment. The authors concluded that children with ANSD can benefit from CIs and their long-term outcomes are similar to their peers with SNHL. The SR by Rajavenkat et al. (2021) was rated critically low in our assessment of the level of evidence and had a high risk of bias in all areas of the ROBIS tool.

CI Outcomes in Children with CND

MRI in the axial and sagittal planes is now routinely conducted for children with SNHL, which allows precisely differentiating cochlear nerve aplasia and hypoplasia. Since the indications for CI have been broadened, currently more patients with CND undergo CIs with varying post-implantation outcomes (Peng et al., 2017). Peng et al. (2017) conducted an SR to determine the factors contributing to speech perception performance in children with CND who underwent CI. Eighteen case studies or case series reporting auditory and speech perception outcomes for 97 children aged at CI operation under 13 years were included in the study. Because of the diversity of outcome measures in the included studies, the authors used the "level of auditory performance"

classification schema to categorize post-CI performance. This classification method, which was originally described by Young et al. (2012), includes four levels from non-stimulation or minimal detection (level 1) to open-set speech perception (level 4). Despite extreme variability across studies in patient characteristics and auditory outcomes, it was concluded that children with cochlear nerve hypoplasia could achieve speech recognition, either closed or open set (65% of the time), more often vs. children with cochlear nerve aplasia (30%). In addition, children with ADs/MCs were more often reported to demonstrate non-stimulation post-CI (43.9%) relative to children without ADs/MCs (8.8%). Although there were a few children with aplasia or partial electrode insertion who could achieve levels of speech discrimination, the presence of a cochlear nerve (hypoplasia vs. aplasia) on MRI and lack of ADs/MCs were reported as predictors of better post-implantation outcomes. In a similar SR of 15 case studies and case series by Vesseur et al. (2018), CI outcomes varied widely in children with CND. Of the total number of 108 children included, 27 (25%) attained "open-set" speech perception, 37 (34%) attained "closed-set" speech perception, and 44 (41%) demonstrated sound detection only. Children with hypoplastic cochlear nerve on MRI were significantly more likely to attain open-set or closed-set speech perception ability compared to children with aplastic cochlear nerve. In addition, although children with cochlear nerve aplasia had a lower chance of successful implantation, some children attained closed-set or open-set levels of speech perception months to years after implantation. These two SRs had several limitations such as the low quality of the included studies without a control group (i.e., case reports and case series) and significant inconsistency in outcome measures. In addition, the overall quality of both SRs was assessed as CL, and they had three or more indications of a high risk of bias in the ROBIS tool. Therefore, it was hard to draw a firm conclusion regarding the auditory and spoken language performance of children with cochlear nerve hypoplasia and aplasia.

Predicting CI Outcomes in Children with ANSD

At present, MRI and routine auditory electrophysiologic tests are common objective tools in identifying ANSD and predicting post-CI outcomes. In postsynaptic ANSD, patients with CND often present with associated labyrinthine abnormalities with various degrees of severity (Peng et al., 2017). Moreover, they are at higher risk of intracranial abnormalities and deficits in the central nervous system (Hall, 2015). In two studies focused on MRI findings, a narrow or obliterated CNC and evidence of CND were predictors of aided hearing thresholds (Kari et al., 2022) or speech perception abilities (Jeong and Kim, 2013). Nonetheless, the MRI technique offers limited spatial resolution and provides no information about the functional status of the auditory pathway. Thus, preoperative MRI results cannot be used as the only criterion for predicting CI outcomes in ANSD (Kutz et al., 2011; Song et al., 2010).

Among routine auditory electrophysiologic assessments, the electrically evoked compound action potential (eCAP) measures the auditory nerve response to electrical stimulation and is similar to the first wave of ABR. Neural response imaging (NRI) or auditory nerve response telemetry (ART) is a technique used to measure eCAP intraoperatively. NRT results within normal limits are an indication of the potential success of the implant and help verify the proper placement and function of electrodes (Cosetti et al., 2010; Sawaf et al., 2022). In Peterson et al. (2003) study, NRT was recorded in all children with ANSD (n=10), and no difference was observed between children with ANSD and peers with SNHL in NRT findings and speech performance scores. In another study on 16 children with ANSD and their peers with SNHL, the two groups performed equally in speech recognition tests in both quiet and noise conditions. However, the ANSD group showed a significant decline in NRT results relative to the control group (Attias et al., 2017).

eABR is another routine auditory electrophysiologic test characterized by three positive peaks (eII, eIII, and eV) generated from the auditory nerve, cochlear nucleus, and perhaps from neurons in the lateral lemniscus or inferior colliculus (Nada et al., 2022). eABR is characterized by larger amplitudes and shorter latencies than acoustic ABR, and it has a steeper latency-intensity function (Firszt et al., 2002; Gordon et al., 2006). Pre-operative eABR can help determine whether the cochlear nerve is electrically excitable, figure out which ear is the most appropriate ear for implantation, identify the site of pathology in ANSD, and provide clinicians with information about the prognosis of CIs (Gibson and Sanli, 2000; Kim et al., 2008). In a study in Australia, Walton et al. (2008) used MRI findings to divide children with ANSD into two groups, including 15 children with CND and 39 children without CND. In this study, intraoperative eABR was abnormal in 87% of children with CND relative to 23% in the control group, and abnormal eABR was found in children with poor speech perception scores in both groups. Compared to children without CND, this study showed a higher rate of abnormal eABR and poor speech perception ability in children with CND (Walton et al., 2008). In Jeon et al. (2013) study, eABR was not recorded in more than half of children with ANSD, and children with ANSD and present eABR showed variability in CI outcomes. Furthermore, in a retrospective study by Yamazaki et al. (2015) on 19 children with CND, both MRI and eABR measures were individually associated with CI outcomes. The authors reported that the combination of MRI and eABR results was a beneficial tool for classifying poor, moderate, and good CI outcomes. Overall, it can be concluded that in infants and young children with ANSD, a combination of MRI and electrophysiologic assessments (i.e., trans-tympanic eCAP and eAR) may provide a reliable prediction of post-CI speech perception performance.

Study Limitations and Directions for Future Research

ANSD is a relatively rare disorder. Approximately one in 7000 neonates evaluated in newborn hearing screening programs is identified with abnormal auditory nerve function (Rance and Starr, 2011; Starr and Rance, 2015). A low sample size of primary studies was a major limitation highlighted in all the included SRs in this review, which might have resulted in overestimating intervention outcomes. All included SRs reported substantial heterogeneity in the primary studies. This high level of variability among primary studies in CI outcomes was not surprising and could originate from a combination of factors such as age at implantation, cognitive and socioeconomic status, comorbid symptoms, and the lesion site (Bo et al., 2022; Riggs et al., 2017). The SRs included in this overview were primarily based on retrospective studies, case reports, case series, and a few prospective reports. Prospective non-randomized cohort studies are an appropriate study design recommended to be used in subsequent similar studies. In evaluating the level of evidence, all but one (Bo et al., 2022) of the SRs were rated as CL. In assessing the risk of bias, except for three SRs (Bo et al., 2022; Chaudhry et al., 2020; Humphriss et al., 2013), other SRs showed a high risk of bias. Thus, the findings of the current overview of SRs should be interpreted with caution. To overcome the current limitations, well-designed, prospective studies, taking into account the role of confounding factors, clarifying the matching criteria, considering sufficient sample sizes, and using valid outcome measures are required. In studies on CI outcome measures, the commonly reported matching criteria are age (date of birth), sex, the onset of hearing loss, age at CI activation, using one or two CIs, and/or duration of CI use (i.e., the follow-up time) (Alzhrani et al., 2019; Breneman et al., 2012; Kang et al., 2010; Rance et al., 2007; Sarankumar et al., 2018); and the known confounding factors related to the outcomes are ADs/MCs, socioeconomic status, and the lesion site (Bo et al., 2022; Riggs et al., 2017). Future research needs

to be clear on the criteria considered for matching a control group for children with ANSD, as well as how the role of confounding factors is taken into account. In addition, the quality of future SRs could be improved by the use of proper tools for assessing the level of evidence and the risk of bias. Likewise, several factors contribute to the quality of upcoming umbrella reviews such as an increased number of relevant high-quality SRs, less heterogeneity in the selected SRs for review, and adding a librarian to the team who could develop a search strategy more consistent with best practices.

Conclusions

The present overview of SRs aimed to systematically summarize and critically appraise current evidence of CI outcomes in children with ANSD, presynaptic or postsynaptic/CND, and to provide directions for future research. According to the reviewed SRs, despite significant variability in children with ANSD, most of these children can achieve CI outcomes comparable to their peers with SNHL. In children with CND, hypoplasia without ADs/MCs is a predictor of better speech performance outcomes compared to aplasia, especially along with additional disabilities or comorbid symptoms. However, except for one study, the overall quality of the included SRs (i.e., the level of evidence) was assessed as CL, and except for three studies, evidence of a high risk of bias was identified in other SRs. To resolve existing limitations and improve the quality of evidence, well-designed, prospective studies with proper sample sizes, using valid outcome measures, clarifying the matching criteria, and taking into account the role of confounding factors are essential.

Conflict of interest: The authors disclose no competing interests.

Acknowledgment: This systematic review was part of a Ph.D. dissertation project in Rehabilitation Sciences, the Audiology and Speech-Language Pathology Program, approved by Ottawa University, Faculty of Health Sciences, School of Rehabilitation Sciences.

Funding: This research was offered funding support from the Ontario Graduate Scholarship (OGS) and the Queen Elizabeth II Scholarships in Science and Technology (QEII-GSST).

Zahra Jafari: Conceptualization (Equal), Writing the first draft of the manuscript (Lead), Conducting systematic search, paper selection, and data extraction (Equal), Review and editing (Equal). **Elizabeth Fitzpatrick:** Review and editing (Equal). **David Schramm:** Review and editing (Equal). **Isabelle Rouillon:** Review and editing (Equal). **Amineh Koravand:** Conceptualization (Equal), Conducting systematic search, paper selection, and data extraction (Equal), Review and editing (Equal).

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author (AK).

References:

Alzhrani, F., Yousef, M., Almuhawas, F., Almutawa, H. (2019). Auditory and speech performance in cochlear implanted ANSD children. *Acta Otolaryngol*. 139(3), 279-283. doi:10.1080/00016489.2019.1571283.

Amin, N., Sethukumar, P., Pai, I., Rajput, K., Nash, R. (2019). Systematic review of cochlear implantation in CHARGE syndrome. *Cochlear Implants Int*. 20(5), 266-280. doi:10.1080/14670100.2019.1634857.

Attias, J., Greenstein, T., Peled, M., Ulanovski, D., Wohlgelernter, J., Raveh, E. (2017). Auditory Performance and Electrical Stimulation Measures in Cochlear Implant Recipients With

Auditory Neuropathy Compared With Severe to Profound Sensorineural Hearing Loss. *Ear Hear*. 38(2), 184-193. doi:10.1097/aud.0000000000000384.

Berlin, C.I., Hood, L.J., Morlet, T., Wilensky, D., Li, L., Mattingly, K.R., Taylor-Jeanfreau, J., Keats, B.J., John, P.S., Montgomery, E., Shallop, J.K., Russell, B.A., Frisch, S.A. (2010). Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-synchrony (auditory neuropathy spectrum disorder). *Int J Audiol*. 49(1), 30-43. doi:10.3109/14992020903160892.

Bo, D., Huang, Y., Wang, B., Lu, P., Chen, W.X., Xu, Z.M. (2022). Auditory and Speech Outcomes of Cochlear Implantation in Children With Auditory Neuropathy Spectrum Disorder: A Systematic Review and Meta-Analysis. *Ann Otol Rhinol Laryngol*, 34894221092201. doi:10.1177/00034894221092201.

Boisvert, I., Reis, M., Au, A., Cowan, R., Dowell, R.C. (2020). Cochlear implantation outcomes in adults: A scoping review. *PLoS One*. 15(5), e0232421. doi:10.1371/journal.pone.0232421.

Brazzelli, M., Cruickshank, M., Tassie, M., McNamee, P., Robertson, C.M., Elders, A., Fraser, C., Hernandez, R., Lawrie, D. (2015). Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture: systematic review and economic evaluation. Appendix 4 Risk-of-bias checklist: non-randomized comparative studies. *Heal Technol Assess (Winch Eng)*. 19(90), 1-202.

Breneman, A.I., Gifford, R.H., Dejong, M.D. (2012). Cochlear implantation in children with auditory neuropathy spectrum disorder: long-term outcomes. *J Am Acad Audiol*. 23(1), 5-17. doi:10.3766/jaaa.23.1.2.

Cant, R., Ryan, C., Kelly, M. (2022). A nine-step pathway to conduct an umbrella review of the literature. *Nurse Author & Editor*. 32(2), 31-34. doi:doi.org/10.1111/nae2.12039.

Chaudhry, D., Chaudhry, A., Muzaffar, J., Monksfield, P., Bance, M. (2020). Cochlear Implantation Outcomes in Post Synaptic Auditory Neuropathies: A Systematic Review and Narrative Synthesis. *J Int Adv Otol*. 16(3), 411-431. doi:10.5152/iao.2020.9035.

Ching, T.Y., Day, J., Dillon, H., Gardner-Berry, K., Hou, S., Seeto, M., Wong, A., Zhang, V. (2013a). Impact of the presence of auditory neuropathy spectrum disorder (ANSD) on outcomes of children at three years of age. *Int J Audiol*. 52 Suppl 2(0 2), S55-64. doi:10.3109/14992027.2013.796532.

Ching, T.Y., Dillon, H., Marnane, V., Hou, S., Day, J., Seeto, M., Crowe, K., Street, L., Thomson, J., Van Buynder, P., Zhang, V., Wong, A., Burns, L., Flynn, C., Cupples, L., Cowan, R.S., Leigh, G., Sjahalam-King, J., Yeh, A. (2013b). Outcomes of early- and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear Hear*. 34(5), 535-552. doi:10.1097/AUD.0b013e3182857718.

Cosetti, M.K., Shapiro, W.H., Green, J.E., Roman, B.R., Lalwani, A.K., Gunn, S.H., Roland, J.T., Jr., Waltzman, S.B. (2010). Intraoperative neural response telemetry as a predictor of performance. *Otol Neurotol*. 31(7), 1095-1099. doi:10.1097/MAO.0b013e3181ec1b8c.

Cupples, L., Ching, T.Y.C., Button, L., Leigh, G., Marnane, V., Whitfield, J., Gunnourie, M., Martin, L. (2018). Language and speech outcomes of children with hearing loss and additional disabilities: identifying the variables that influence performance at five years of age. *Int J Audiol*. 57(sup2), S93-s104. doi:10.1080/14992027.2016.1228127.

Daneshi, A., Mirsalehi, M., Hashemi, S.B., Ajalloueyan, M., Rajati, M., Ghasemi, M.M., Emamdjomeh, H., Asghari, A., Mohammadi, S., Mohseni, M., Mohebbi, S., Farhadi, M.

(2018). Cochlear implantation in children with auditory neuropathy spectrum disorder: A multicenter study on auditory performance and speech production outcomes. *Int J Pediatr Otorhinolaryngol*. 108, 12-16. doi:10.1016/j.ijporl.2018.02.004.

Fernandes, N.F., Morettin, M., Yamaguti, E.H., Costa, O.A., Bevilacqua, M.C. (2015). Performance of hearing skills in children with auditory neuropathy spectrum disorder using cochlear implant: a systematic review. *Braz J Otorhinolaryngol*. 81(1), 85-96. doi:10.1016/j.bjorl.2014.10.003.

Firszt, J.B., Chambers, R.D., Kraus, Reeder, R.M. (2002). Neurophysiology of cochlear implant users I: effects of stimulus current level and electrode site on the electrical ABR, MLR, and N1-P2 response. *Ear Hear*. 23(6), 502-515. doi:10.1097/00003446-200212000-00002

Gibson, W., Sanli, H., 2000. The role of round window electrophysiological techniques in the selection of children for cochlear implants. In: Kim, C., Chang, S., Lim, D. (Eds.), Advances in Oto-Rhino-Laryngology. Karger, Basel, pp. 148-151.

Gibson, W.P., Sanli, H. (2007). Auditory neuropathy: an update. *Ear Hear*. 28(2 Suppl), 102s-106s. doi:10.1097/AUD.0b013e3180315392.

Gordon, K.A., Papsin, B.C., Harrison, R.V. (2006). An evoked potential study of the developmental time course of the auditory nerve and brainstem in children using cochlear implants. *Audiol Neurootol*. 11(1), 7-23. doi:10.1159/000088851.

Hall, J., 2015. eHandbook of Auditory Evoked Responses: Principles, Procedures & Protocols. Pearson Education, Inc.

He, S., Grose, J., Teagle, H., Woodard, J., Park, L., Hatch, D., Roush, P., Buchman, C. (2015). Acoustically evoked auditory change complex in children with auditory neuropathy

spectrum disorder: a potential objective tool for identifying cochlear implant candidates. *Ear Hear*. 36(3), 289-301. doi:10.1097/aud.0000000000000119.

He, W., Wang, M., Jiang, L., Li, M., Han, X. (2019). Cognitive interventions for mild cognitive impairment and dementia: An overview of systematic reviews. *Complement Ther Med*. 47, 102199. doi:10.1016/j.ctim.2019.102199.

Higgins, J., Green, S. (2013). Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. *The Cochrane Collaboration*.

Humphriss, R., Hall, A., Maddocks, J., Macleod, J., Sawaya, K., Midgley, E. (2013). Does cochlear implantation improve speech recognition in children with auditory neuropathy spectrum disorder? A systematic review. *Int J Audiol*. 52(7), 442-454. doi:10.3109/14992027.2013.786190.

Jeon, J.H., Bae, M.R., Song, M.H., Noh, S.H., Choi, K.H., Choi, J.Y. (2013). Relationship between electrically evoked auditory brainstem response and auditory performance after cochlear implant in patients with auditory neuropathy spectrum disorder. *Otol Neurotol*. 34(7), 1261-1266. doi:10.1097/MAO.0b013e318291c632.

Jeong, S.W., Kim, L.S. (2013). Auditory neuropathy spectrum disorder: predictive value of radiologic studies and electrophysiologic tests on cochlear implant outcomes and its radiologic classification. *Acta Otolaryngol*. 133(7), 714-721. doi:10.3109/00016489.2013.776176.

Kang, W.S., Lee, J.H., Lee, H.N., Lee, K.S. (2010). Cochlear implantations in young children with cochlear nerve deficiency diagnosed by MRI. *Otolaryngol Head Neck Surg*. 143(1), 101-108. doi:10.1016/j.otohns.2010.03.016.

Kari, E., Gillard, D.M., Chuang, N., Go, J.L. (2022). Can Imaging Predict Hearing Outcomes in Children With Cochleovestibular Nerve Abnormalities? *Laryngoscope*. 132 Suppl 8, S1-s15. doi:10.1002/lary.30008.

Kim, A.H., Kileny, P.R., Arts, H.A., El-Kashlan, H.K., Telian, S.A., Zwolan, T.A. (2008). Role of electrically evoked auditory brainstem response in cochlear implantation of children with inner ear malformations. *Otol Neurotol*. 29(5), 626-634. doi:10.1097/MAO.0b013e31817781f5.

Kutz, J.W., Jr., Lee, K.H., Isaacson, B., Booth, T.N., Sweeney, M.H., Roland, P.S. (2011). Cochlear implantation in children with cochlear nerve absence or deficiency. *Otol Neurotol*. 32(6), 956-961. doi:10.1097/MAO.0b013e31821f473b.

Leigh, J., Dettman, S., Dowell, R., Sarant, J. (2011). Evidence-based approach for making cochlear implant recommendations for infants with residual hearing. *Ear Hear*. 32(3), 313-322. doi:10.1097/AUD.0b013e3182008b1c.

Liu, Y., Dong, R., Li, Y., Xu, T., Li, Y., Chen, X., Gong, S. (2014). Effect of age at cochlear implantation on auditory and speech development of children with auditory neuropathy spectrum disorder. *Auris Nasus Larynx*. 41(6), 502-506. doi:10.1016/j.anl.2014.06.001.

Madden, C., Rutter, M., Hilbert, L., Greinwald, J.H., Jr., Choo, D.I. (2002). Clinical and audiological features in auditory neuropathy. *Arch Otolaryngol Head Neck Surg*. 128(9), 1026-1030. doi:10.1001/archotol.128.9.1026.

Mason, J.C., De Michele, A., Stevens, C., Ruth, R.A., Hashisaki, G.T. (2003). Cochlear implantation in patients with auditory neuropathy of varied etiologies. *Laryngoscope*. 113(1), 45-49. doi:10.1097/00005537-200301000-00009.

Merkus, P., Di Lella, F., Di Trapani, G., Pasanisi, E., Beltrame, M.A., Zanetti, D., Negri, M., Sanna, M. (2014). Indications and contraindications of auditory brainstem implants: systematic review and illustrative cases. *Eur Arch Otorhinolaryngol*. 271(1), 3-13. doi:10.1007/s00405-013-2378-3.

Methley, A.M., Campbell, S., Chew-Graham, C., McNally, R., Cheraghi-Sohi, S. (2014). PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res*. 14, 579. doi:10.1186/s12913-014-0579-0.

Myers, K., Nicholson, N. (2021). Cochlear Implant Behavioral Outcomes for Children With Auditory Neuropathy Spectrum Disorder: A Mini-Systematic Review. *Am J Audiol*. 30(3), 777-789. doi:10.1044/2021_aja-20-00175.

Nada, N., Kolkaila, E., Schendzielorz, P., El Mahallawi, T. (2022). Electrically evoked auditory brainstem response in cochlear implantation: what you need to know (short review). *The Egyptian Journal of Otolaryngology*. 38(67), 1-8. doi:doi.org/10.1186/s43163-022-00259-1.

Niparko, J.K., Tobey, E.A., Thal, D.J., Eisenberg, L.S., Wang, N.Y., Quittner, A.L., Fink, N.E. (2010). Spoken language development in children following cochlear implantation. *Jama*. 303(15), 1498-1506. doi:10.1001/jama.2010.451.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P.,

Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 134, 178-189. doi:10.1016/j.jclinepi.2021.03.001.

Peng, K.A., Kuan, E.C., Hagan, S., Wilkinson, E.P., Miller, M.E. (2017). Cochlear Nerve Aplasia and Hypoplasia: Predictors of Cochlear Implant Success. *Otolaryngol Head Neck Surg*. 157(3), 392-400. doi:10.1177/0194599817718798.

Peterson, A., Shallop, J., Driscoll, C., Breneman, A., Babb, J., Stoeckel, R., Fabry, L. (2003). Outcomes of cochlear implantation in children with auditory neuropathy. *J Am Acad Audiol*. 14(4), 188-201.

Pollock, M., Fernandes, R., Becker, L., Pieper, D., Hartling, L., 2022. Chapter V: Overviews of Reviews. Cochrane Traning. In: Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., Welch, V. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions. Online, Version 6.3, 2022. Cochrane.

Rajavenkat, S., Umashankar, A., Chandrasekaran, P. (2021). Bionic Hearing in Auditory Neuropathy Spectrum Disorder: A Systematic Review. *Indian Journal of Otology*. 27, 169-179.

Rajput, K., Saeed, M., Ahmed, J., Chung, M., Munro, C., Patel, S., Leal, C., Jiang, D., Nash, R. (2019). Findings from aetiological investigation of Auditory Neuropathy Spectrum Disorder in children referred to cochlear implant programs. *Int J Pediatr Otorhinolaryngol*. 116, 79-83. doi:10.1016/j.ijporl.2018.10.010.

Rance, G., Barker, E.J. (2009). Speech and language outcomes in children with auditory neuropathy/dys-synchrony managed with either cochlear implants or hearing aids. *Int J Audiol*. 48(6), 313-320. doi:10.1080/14992020802665959.

Rance, G., Barker, E.J., Sarant, J.Z., Ching, T.Y. (2007). Receptive language and speech production in children with auditory neuropathy/dyssynchrony type hearing loss. *Ear Hear*. 28(5), 694-702. doi:10.1097/AUD.0b013e31812f71de.

Rance, G., McKay, C., Grayden, D. (2004). Perceptual characterization of children with auditory neuropathy. *Ear Hear*. 25(1), 34-46. doi:10.1097/01.aud.0000111259.59690.b8.

Rance, G., Starr, A., 2011. Auditory neuropathy/dys-synchrony. In: Seewald, R., Tharpe, A. (Eds.), Comprehensive handbook of pediatric audiology Plural Publishing, San Diego, pp. 225-242.

Rance, G., Starr, A. (2015). Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. *Brain*. 138(Pt 11), 3141-3158. doi:10.1093/brain/awv270.

Riggs, W.J., Roche, J.P., Giardina, C.K., Harris, M.S., Bastian, Z.J., Fontenot, T.E., Buchman, C.A., Brown, K.D., Adunka, O.F., Fitzpatrick, D.C. (2017). Intraoperative Electrocochleographic Characteristics of Auditory Neuropathy Spectrum Disorder in Cochlear Implant Subjects. *Front Neurosci*. 11, 416. doi:10.3389/fnins.2017.00416.

Roche, J.P., Huang, B.Y., Castillo, M., Bassim, M.K., Adunka, O.F., Buchman, C.A. (2010). Imaging characteristics of children with auditory neuropathy spectrum disorder. *Otol Neurotol*. 31(5), 780-788. doi:10.1097/mao.0b013e3181d8d528.

Rødvik, A.K., von Koss Torkildsen, J., Wie, O.B., Storaker, M.A., Silvola, J.T. (2018). Consonant and Vowel Identification in Cochlear Implant Users Measured by Nonsense Words: A Systematic Review and Meta-analysis. *J Speech Lang Hear Res*. 61(4), 1023-1050. doi:10.1044/2018_jslhr-h-16-0463.

Roush, P., Frymark, T., Venediktov, R., Wang, B. (2011). Audiologic management of auditory neuropathy spectrum disorder in children: a systematic review of the literature. *Am J Audiol*. 20(2), 159-170. doi:10.1044/1059-0889(2011/10-0032).

Santarelli, R., Rossi, R., Scimemi, P., Cama, E., Valentino, M.L., La Morgia, C., Caporali, L., Liguori, R., Magnavita, V., Monteleone, A., Biscaro, A., Arslan, E., Carelli, V. (2015). OPA1-related auditory neuropathy: site of lesion and outcome of cochlear implantation. *Brain*. 138(Pt 3), 563-576. doi:10.1093/brain/awu378.

Santarelli, R., Scimemi, P., La Morgia, C., Cama, E., Del Castillo, I., Carelli, V. (2021). Electrocochleography in Auditory Neuropathy Related to Mutations in the OTOF or OPA1 Gene. *Audiol Res*. 11(4), 639-652. doi:10.3390/audiolres11040059.

Sarankumar, T., Arumugam, S.V., Goyal, S., Chauhan, N., Kumari, A., Kameswaran, M. (2018). Outcomes of Cochlear Implantation in Auditory Neuropathy Spectrum Disorder and the Role of Cortical Auditory Evoked Potentials in Benefit Evaluation. *Turk Arch Otorhinolaryngol*. 56(1), 15-20. doi:10.5152/tao.2017.2537.

Sawaf, T., Vovos, R., Hadford, S., Woodson, E., Anne, S. (2022). Utility of intraoperative neural response telemetry in pediatric cochlear implants. *Int J Pediatr Otorhinolaryngol*. 162, 111298. doi:10.1016/j.ijporl.2022.111298.

Shafiro, V., Luzum, N., Moberly, A.C., Harris, M.S. (2021). Perception of Environmental Sounds in Cochlear Implant Users: A Systematic Review. *Front Neurosci*. 15, 788899. doi:10.3389/fnins.2021.788899.

Shallop, J. (2002). Auditory neuropathy/dys-synchrony in adults and children. *Sem Hear*(23), 215-223.

Shea, B.J., Reeves, B.C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E., Henry, D.A. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both. *Bmj*. 358, j4008. doi:10.1136/bmj.j4008.

Shearer, A.E., Hansen, M.R. (2019). Auditory synaptopathy, auditory neuropathy, and cochlear implantation. *Laryngoscope Investig Otolaryngol*. 4(4), 429-440. doi:10.1002/lio2.288

Song, M.H., Bae, M.R., Kim, H.N., Lee, W.S., Yang, W.S., Choi, J.Y. (2010). Value of intracochlear electrically evoked auditory brainstem response after cochlear implantation in patients with narrow internal auditory canal. *Laryngoscope*. 120(8), 1625-1631. doi:10.1002/lary.21008.

Starr, A., Rance, G., 2015. Auditory neuropathy. In: Celesia, G., Hickok, G. (Eds.), Handbook of Clinical Neurology. Elsevier, Edinburgh pp. 495-508.

Teagle, H.F., Roush, P.A., Woodard, J.S., Hatch, D.R., Zdanski, C.J., Buss, E., Buchman, C.A. (2010). Cochlear implantation in children with auditory neuropathy spectrum disorder. *Ear Hear*. 31(3), 325-335. doi:10.1097/AUD.0b013e3181ce693b.

Vesseur, A., Free, R., Snels, C., Dekker, F., Mylanus, E., Verbist, B., Frijns, J. (2018). Hearing Restoration in Cochlear Nerve Deficiency: the Choice Between Cochlear Implant or Auditory Brainstem Implant, a Meta-analysis. *Otol Neurotol*. 39(4), 428-437. doi:10.1097/mao.0000000000001727.

Walton, J., Gibson, W.P., Sanli, H., Prelog, K. (2008). Predicting cochlear implant outcomes in children with auditory neuropathy. *Otol Neurotol*. 29(3), 302-309. doi:10.1097/MAO.0b013e318164d0f6.

Whiting, P., Rutjes, A., Westwood, M., Mallett, S., Deeks, J., Reitsma, J., Leeflang, M., Sterne, J., Bossuyt, P. (2011). QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 155(8), 529-536. doi:10.7326/0003-4819-155-8-201110180-00009.

Whiting, P., Savović, J., Higgins, J.P., Caldwell, D.M., Reeves, B.C., Shea, B., Davies, P., Kleijnen, J., Churchill, R. (2016). ROBIS: A new tool to assess the risk of bias in systematic reviews was developed. *J Clin Epidemiol*. 69, 225-234. doi:10.1016/j.jclinepi.2015.06.005

Yamazaki, H., Leigh, J., Briggs, R., Naito, Y. (2015). Usefulness of MRI and EABR Testing for Predicting CI Outcomes Immediately After Cochlear Implantation in Cases With Cochlear Nerve Deficiency. *Otol Neurotol*. 36(6), 977-984. doi:10.1097/mao.0000000000000721.

Young, N.M., Kim, F.M., Ryan, M.E., Tournis, E., Yaras, S. (2012). Pediatric cochlear implantation of children with eighth nerve deficiency. *Int J Pediatr Otorhinolaryngol*. 76(10), 1442-1448. doi:10.1016/j.ijporl.2012.06.019.

Zeng, F.G., Liu, S. (2006). Speech perception in individuals with auditory neuropathy. *J Speech Lang Hear Res*. 49(2), 367-380. doi:10.1044/1092-4388(2006/029).

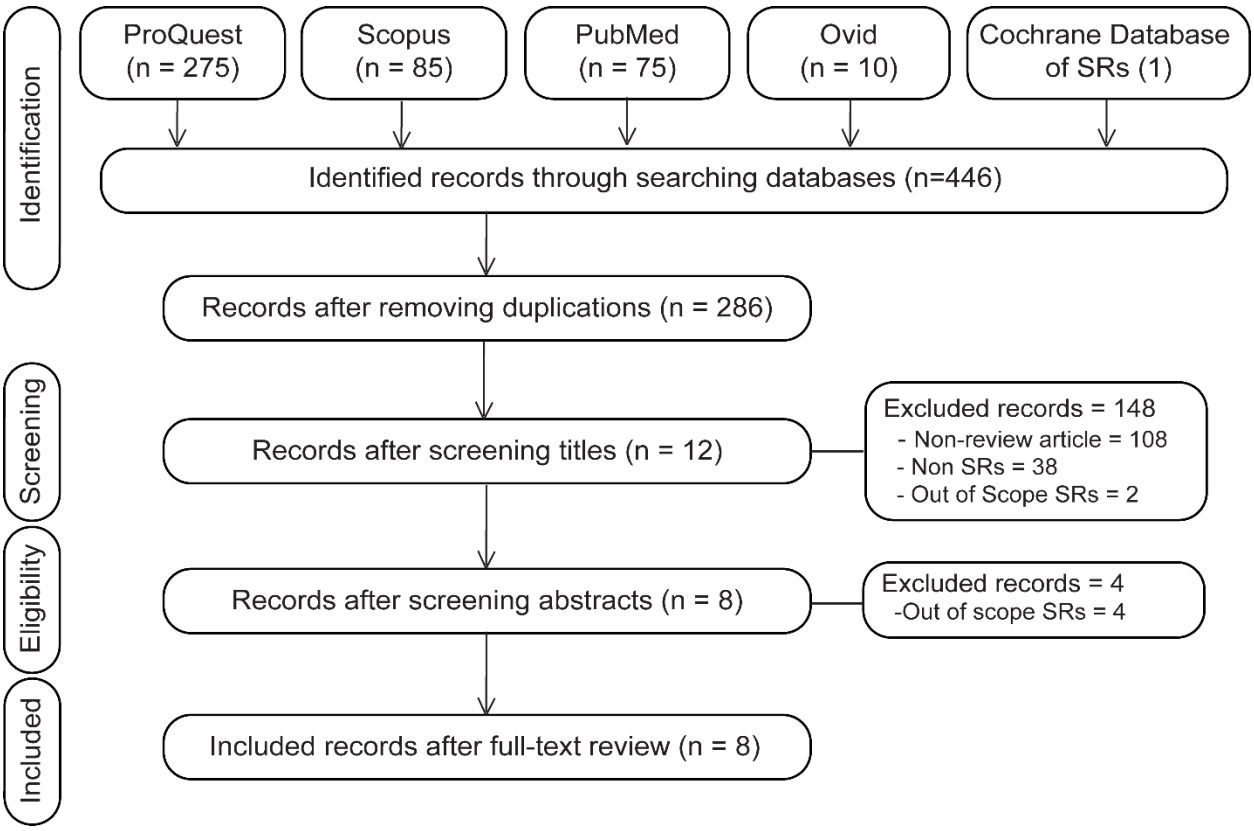

Figure 1. The PRISMA flow diagram illustrates how the literature search and screening process was summarized. According to PICOS, excluded records were those that did not meet the inclusion criteria. PICOS, capital letters represent participants, intervention(s), comparators, outcomes, and study designs, respectively. PRISMA: preferred reporting items for systematic reviews and meta-analyses.

Table 1. Characteristics of the included systematic reviews

Study	Year	Country	Language [a]	Databases searched	Number of included studies	Total sample size of primary studies	Age at CIs (year)[b]	Study design	Quality assessment tool	Outcome measures	Results
Bo et al.	2022	China	No limitation	PubMed, Embase, Web of Science	15	ANSD=259 SNHL=408	3.22	Retrospective, prospective	RoB, Modified NOS	CAP, SIR, open-set SP	Children with ANSD achieve auditory and speech performance outcomes comparable to their peers with SNHL.
Chaudhry et al.	2020	The UK	NR	PubMed, Web of Science, Cochrane Library	14	ANSD=32	38.6 (4-70)	Case reports or case series	Brazeli RoB tool for non-RCT	Several phonemic detection and SP tests (open-set or closed-set)	Children with postsynaptic ANSD demonstrate variability in CI outcomes, but overall show improvements in hearing thresholds and speech perception.
Fernandes et al.	2015	Brazil	English, Spanish, or Portuguese	PubMed, SciELO, Cochrane Library, LILACS, Embase, etc.	20	ANSD=NR SNHL=NR	Children, age NR	All types of articles except case reports and reviews	NR	Open-set SP tests, GASP, MAIS, IT-MAIS, HINT	Children with ANSD achieve CI outcomes equal to their peers with SNHL.
Humphriss et al.	2013	The UK	English	PubMed, CINAHL, Web of Science, Google Scholar	27 (12 studies had a control group.)	ANSD=184 SNHL=332	1-13	Cross-sectional, case-control, case series,	Bond et al. 2009 [c]	A wide range of SP tests	Children with ANSD can benefit from CIs.

								case studies			
Myers & Nicholson	2021	USA	English	PubMed, CINAHL	4	ANSD=211[d]	2.45	Prospective, case series	JBI	CAP, SIR, CDI, DEAP, PLS-4, PPVT-4, MUSS, LNT, MLNT, MAIS, IT-MAIS, PEACH	Despite the ANSD heterogeneity, children with ANSD achieve CI outcomes equivalent to their peers with SNHL.
Peng et al.	2017	USA	English	PubMed, Web of Science, Cochrane Library, Google Scholar	18	CND=97	3.7(1.6-5.1)	Case reports, case series	NR	Classifying the outcomes according to the “level of auditory performance" classification scale	Children with hypoplasia are more likely to achieve speech discrimination compared to children with aplasia. The absence of comorbid syndromes is associated with better CI performance.
Rajavenkat et al.	2021	India	English	PubMed, Google Scholar, EBSCO, Web of Science, etc.	9	ANSD=291	Children, age NR	Retrospective, prospective	QUADAS 2	SP scores, CAP, some questionnaires	CI is beneficial for children with ANSD.
Vesseur et al.	2018	The Netherlands	English	PubMed, Cochrane Library	15	CND=108	1.66-5.16	Case reports, case series	NR	Sound and SP tests, open or closed sets, and some questionnaires	CI has no contraindications in children with CND. Children with hypoplasia achieve better outcomes compared to children with aplasia.

ANSD: auditory neuropathy spectrum disorder, CAP: categories of auditory performance, CDI: child development inventory, CI: cochlear implant, DEAP: diagnostic evaluation of articulation and phonology, GASP: Glendonald auditory screening procedure, HINT: hearing in noise test, JBI: Joanna Briggs Institute, IT-MAIS: infant–toddler meaningful auditory integration scale, LNT: lexical noise Test, MAIS: meaningful auditory integration scale, MLNT: multisyllabic lexical noise test, MUSS: meaningful use of speech scale, NOS: Newcastle-Ottawa Scale, NR: not reported, PEACH: parents evaluation of aural/oral performance of children, PLS-4: preschool language scale–fourth edition, PPVT-4: Peabody picture vocabulary test fourth edition, RCT: randomized controlled trials, RoB: risk of bias, QUADAS: quality assessment of diagnostic accuracy studies, SIR: speech intelligibility rating, SNHL: sensory neural hearing loss, SP: speech perception.

[a] The language of publications considered for the systematic search.

[b] The mean and/or range of age reported at the time of CI activation.

[c] A quality assessment tool, previously used by Bond et al (2009) in a systematic review of the effectiveness of CI for severe to profound hearing loss.

[d] Of the four studies, two had a control group (SNHL), and two compared children with age at CIs before and after 24 months of age.

Table 2. Critical appraisal of included studies using the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) checklist

Study	**Year**	Q1	**Q2**	Q3	**Q4**	Q5	Q6	**Q7**	Q8	**Q9**	Q10	**Q11**	Q12	**Q13**	Q14	**Q15**	Q16	**Overall quality**
Bo et al.	2022	1[a]	0.5	1	1	1	1	0	1	1	1	1	1	1	1	1	1	L[b]
Chaudhry et al.	2020	1	1	1	1	1	1	0	1	1	0	0	0	1	1	1	0	CL
Fernandes et al.	2015	1	0	1	0	1	0	0	1	0	1	0	0	0	0	0	1	CL
Humphriss et al.	2013	1	0.5	1	0.5	1	0	0	1	0.5	0	0	0	1	0	0	1	CL
Myers & Nicholson	2021	1	0.5	1	1	1	0	0	1	0.5	0	0	0	1	1	0	1	CL
Peng et al.	2017	0	0	1	0	1	0	0	1	0	1	0	0	0	0	0	1	CL
Rajavenkat et al.	2021	0	0.5	1	0.5	1	0	0.5	1	0	0	0	0	0	0	0	1	CL
Vesseur et al.	2018	0	0	0	0.5	0	0	0	1	0	1	0	0	0	0	0	1	CL
N(%)		5 (62.5)	3 (37.5)	7 (87.5)	4.5 (56.2)	7 (87.5)	2 (25.0)	0 (0.0)	0.5 (100)	3 (6.2)	4 (50.0)	1 (12.5)	1 (12.5)	4 (50.0)	3 (37.5)	2 (25.0)	7 (87.5)	

*Critical questions were shown bolded (i.e., Q2, Q4, Q7, Q9, Q11, Q13, and Q15).

[a] The rating scale for items 2, 4, 7, 8, 9, 11, 12, and 15 was yes = 1, partial yes = 0.5, and no = 0. The rating scale for items 1, 3, 5, 6, 10, 13, 14, and 16 was yes = 1 and no = 0.

[b] Overall rating: High (H): no or one non-critical weakness; Moderate (M): more than one non-critical weakness; Low (L): one critical flaw with or without non-critical weaknesses; and Critically Low (CL): more than one critical flaw with or without non-critical weaknesses (Shea et al., 2017).

Table 3. Risk of bias assessment using the Risk of Bias in Systematic Reviews (ROBIS) tool

		Phase 2				Phase 3
Study	**Year**	1. Study eligibility criteria	2. Identification & selection of studies	3. Data collection & study appraisal	4. Synthesis and findings	Risk of bias in the systematic review
Bo et al.	2022	☺	☺	☺	☺	☺
Chaudhry et al.	2020	☺	☺	☺	☺	☺
Fernandes et al.	2015	☺	☹	☹	☹	☹
Humphriss et al.	2013	☺	☺	☺	☺	☺
Myers & Nicholson	2021	☹	☹	☺	☹	☺
Peng et al.	2017	☺	☹	☹	☺	☹
Rajavenkat et al.	2021	☹	☹	☹	☹	☹
Vesseur et al.	2018	☹	☹	☹	☹	☹

☺= low risk, ☹= high risk, ? = unclear risk (Whiting et al., 2016).

Appendix A

The PICOS Framework

PICOS framework used for selecting SRs in the present umbrella review

PICOS	Description
Population	SRs of children diagnosed with presynaptic or postsynaptic ANSD
Intervention	Use of one or two CIs
Comparator	Children with SNHL (matched based on the date of birth, sex, age at CI activation, and/or other factors) or no control group.
Outcome	Auditory, speech, and/or language test scores and/or findings from relevant questionnaires
Study design	SRs with or without statistical analysis (i.e., meta-analysis).

ANSD: auditory neuropathy spectrum disorder, CI: cochlear implant, PICOS stands for participants, intervention(s), comparators, outcomes, and study designs, SNHL: sensorineural hearing loss, SR: systematic review.

Appendix B

Search Strategy

The search strategy with MeSH terms in the present overview of systematic reviews

Electronic databases searched: ProQuest, PubMed, Scopus, Ovid, and the Cochrane Database of Systematic Reviews

Search time frame: From electronic databases' inception to November 2022

Key terms: Using the following combined search terms:

(a) "auditory neuropathy" (MeSH: auditory neuropathy) AND "cochlear implant" (MeSH: cochlear implants) AND "outcome" (MeSH: patient outcome assessment) AND "review" (MeSH: systematic review [publication type])

(b) "cochlear nerve deficiency" OR "aplasia" (MeSH: abnormalities) OR "hypoplasia" (MeSH: hypoplasia) AND "cochlear implant" (MeSH: cochlear implants) AND "outcome" (MeSH: patient outcome assessment) AND "review" (MeSH: systematic review [publication type])

Search restrictions: The search had no restrictions on language, publication status, or year of publication.

Search for missing articles: References to included studies were manually checked for missing articles in the database search. No further related articles, however, were found.

Top-up search (April 2023): The database search was rerun to include any studies published between December 2022 and April 2023. No additional systematic reviews, however, were found.

MeSH: medical subject heading

Chapter 5

General Conclusions

ANSD is a complex disorder with no uniform approach to appropriately managing the needs of every child affected (Rance and Starr, 2015). Depending on the etiology involved, ANSD shows a heterogeneous clinical profile leading to diagnostic and therapeutic challenges. A variety of etiologies contribute to ANSD (e.g., syndromic and non-syndromic abnormalities and perinatal or pre-lingual factors) (Saidia et al., 2023), which provides an explanation for variable prognosis and inconsistent response to therapeutic interventions in children with ANSD (James et al., 2020). While other children with hearing thresholds within or close to normal limits may benefit from assistive listening devices, some require HAs or CIs to facilitate speech and language development (James et al., 2020). Due to this heterogeneity in children with ANSD, families need adequate information about HL characteristics, auditory and non-auditory assessments required, test results interpretation, hearing device technologies, and available intervention options (Myers and Nicholson, 2021; Walker et al., 2016; Wolfe, 2020).

This doctoral thesis, consisting of three associated projects, aimed to study the predictors of CI outcomes in children with ANSD. This chapter summarizes the findings of the three studies, draws grand conclusions, and addresses the clinical implications and limitations of existing evidence. The first project of this doctoral thesis aimed to determine the relationship between age

at HL diagnosis, age at HA and CI activation, and the length of follow-up with CI/HA and open-set speech perception test scores; and to identify factors with predictive value for post-implantation outcomes. We reviewed the records of all children with ANSD (n = 38) at the Children's Hospital of Eastern Ontario (CHEO), who were identified between 2000 and 2022 and used CIs and/or HAs. In children with congenital or early-onset hearing loss (HL), a significant difference was observed between ages at HL diagnosis (5.68 months) and CI activation (29.43 months), and factors such as NICU admission, PB, and the presence of ADs/MCs had no significant impact on ages at HL diagnosis, HA fitting, and CI activation. These three critical ages in our study were comparable with the ages reported in past studies on children with ANSD ANSD (Budenz et al., 2013; Ching et al., 2013a; Kontorinis et al., 2014) or SNHL (Budenz et al., 2013; Ching et al., 2013b; Fitzpatrick et al., 2011; Harrison and Roush, 1996; Jafari et al., 2007; Kittrell and Arjmand, 1997; le Roux et al., 2016; Ozcebe et al., 2005; Prendergast et al., 2002). In the correlational analysis, earlier ages at HL diagnosis and CI activation, and a longer duration of follow-up with CI/HA were significantly associated with improved speech perception outcomes. In addition, among ten variables (e.g., age of HL diagnosis, age at fitting HAs, age at CI activation, follow-up period, the onset of HL, use of one or two CIs, NICU history, preterm birth, ADs/MCs, and sex) included in the Forward Linear multiple Regression Model, the length of follow-up with CI/HA and bilateral amplification showed prognostic value for open-set speech perception outcomes (i.e., PBK and HINT test scores). These findings were aligned with previous studies on children with congenital or prelingual HL demonstrating the negative impact of auditory deprivation and the positive effect of long-term hearing amplification use on spoken language development (Kral et al., 2019; Kral and Sharma, 2012; Sharma and Campbell, 2011; Yoshinaga-Itano et al., 1998). Our findings suggest that in children with ANSD, lower ages of HL diagnosis and CI activation, longer

duration of CI/HA use, and the use of two CIs/HAs are associated with improved intervention outcomes. However, this retrospective study had several limitations including missing data on speech perception test scores (i.e., outcome measures: PBK-W/P and HINT in quiet and noise conditions) and a lack of information about other potential factors contributing to speech perception outcomes, such as socioeconomic status, maternal education, and mode of communication at home. To resolve these limitations, well-designed prospective studies with appropriate sample sizes are needed.

In addition to demographic, child-related, health-related, and socioeconomic factors that might predict long-term intervention outcomes (Ching et al., 2013b; le Roux et al., 2016; Omar et al., 2022), auditory electrophysiologic and imaging results are objective variables with prognostic value for CI outcomes. The second project of this doctoral thesis aimed to systematically summarize and critically appraise existing evidence of the prognostic value of early electrophysiologic (intraoperative and/or postoperative eCAP and eABR) and preoperative MRI findings for CI outcomes. Of the 25 included studies, the relevance of eCAP, eABR, and/or MRI findings to CI outcomes was reported in 10, 11, and 11 studies, respectively. We used the Crowe Critical Appraisal Tool (CCAT) and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to assess methodological quality and strength of evidence, respectively. While the predictive value of eCAP findings for CI outcomes was uncertain, the presence of eABR and no evidence of CND (especially aplasia) in MRI were indicative of better post-CI speech perception outcomes. This finding may help clinicians with decision-making about CI candidacy and consultation with the family. However, in this SR, substantial heterogeneity was identified among selected studies in chronological age, age at CI activation, the length of follow-up with CI/HA, and outcome measures, which might have affected our conclusions. This

heterogeneity did not allow us to conduct meta-analyses, leading to narratively synthesizing and interpreting the findings. The included studies had several limitations such as an observational design commonly with no control group, and low sample sizes in most studies, which put studies at risk of overestimating intervention outcomes (i.e., small study bias/effect) (Button et al., 2013; Turner et al., 2013). In addition, the studies were limited in taking into account the role of other potential contributors to the outcomes, especially ADs/MCs (Bo et al., 2022; Ching et al., 2013a; le Roux et al., 2016). Therefore, caution should be taken in interpreting the findings.

During the past two decades, several SRs have been published on CI outcomes in children with ANSD (Bo et al., 2022; Humphriss et al., 2013; Myers and Nicholson, 2021; Peng et al., 2017; Rance and Starr, 2015; Vesseur et al., 2018). The objective of the third project of this doctoral thesis was to systematically overview, summarize, and critically appraise current SRs of CI outcomes in children with ANSD, and provide directions for future research. We used the AMSTAR-2 checklist and the ROBIS tool to assess the methodological quality and the risk of bias in the included SRs, respectively. According to the eight included SRs, despite significant variability in children with ANSD, they often achieve CI outcomes comparable to their peers with SNHL. In children with postsynaptic ANSD (evidence of CND), hypoplasia without ADs/MCs is associated with better speech performance outcomes than aplasia and the presence of ADs/MCs. However, the methodological quality of most selected SRs was evaluated as critically low with a high risk of bias due to the limitations of primary studies included in the SRs, especially low sample sizes, and poor study designs. The SRs reported substantial inconsistency in primary studies in several factors such as the lesion site, age at implantation, cognitive and socioeconomic status, and ADs/MCs (Bo et al., 2022; Riggs et al., 2017). Future studies with a well-designed, randomized/prospective research design, taking into account the role of confounding factors,

clarifying the matching criteria, considering appropriate sample sizes, and using valid outcome measures could help improve evidence quality, and assist with decision-making and consultation in clinical settings. The quality of the SRs could also be improved by using proper appraisal tools to assess the risk of bias and the quality of evidence. Therefore, the findings of this umbrella review should be interpreted with caution. SRs.

Electrode-neuron interface (ENI) is a phenomenon that may play a role in poor speech perception outcomes in children with aplasia. ENI is a situation in which an activated channel stimulates more distant neurons in the cochlea, resulting in overlaps in electrode activation (Bierer, 2010). ENI causes intrasubject channel-to-channel variability in CI thresholds and most comfortable levels (MCLs), which can negatively affect speech perception outcomes (Bierer and Faulkner, 2010; Pfingst et al., 2008). In the clinical setting, ENI occurs more frequently in channels with relatively high thresholds than in channels with relatively low thresholds (Bierer and Middlebrooks, 2002). It is characterized by broader psychophysical tuning curves and smaller dynamic ranges (Bierer and Faulkner, 2010). CI electrodes with high thresholds are commonly observed in bipolar (consisting of both active and return electrodes in the Scala tympani, usually separated by one or more inactive electrodes) and tripolar (including an intra-scalar active electrode and two adjacent electrodes sharing the return current equally) electrode configurations, as opposed to monopolar electrode configurations (with one intra-scalar electrode as the active electrode and an extracochlear electrode as the return) (Bierer and Middlebrooks, 2002; Snyder et al., 2008). Changes in these subjective hearing and speech perceptions can lead to increased difficulty in intensity-based information discrimination, particularly in the presence of competing noise .(Bierer, 2010)

Limitations and Implications for Future Research

In summary, the findings of our retrospective chart review, describing the role of several key contributing factors to open-set speech perception performance, could be useful for health-related professionals in decision-making for EHDI, and in counseling or guiding parents of children with HL, especially those who are candidates for CIs. The findings of our two SRs indicate that eABR and MRI findings are strong predictors of post-CI speech perception outcomes; children with presynaptic ANSD can achieve speech perception performance equal to peers with SNHL; and in children with CND, aplasia, especially along with ADs/MCs, is associated with poor CI outcomes. These findings help clinicians guide families about the interpretation of MRI and electrophysiologic findings, potential expectations from hearing technology options, and decision-making for CI candidacy.

Our findings, however, indicate limitations of existing studies, especially in study design (mostly small retrospective studies with no control group), taking into account the role of major contributors to the outcomes (e.g., ADs/MCs, socioeconomic status, maternal education, genetic background, etc.), and heterogeneity in participants. These limitations affect the studies' quality and make it challenging to draw firm conclusions. Well-designed studies could improve evidence quality leading to improved quality of evidence in reviews grounded on a systematic search, and support decision-making and consultation in clinical settings.

References:

Bierer, J.A. (2010). Probing the electrode-neuron interface with focused cochlear implant stimulation. *Trends Amplif*. 14(2), 84-95. doi:10.1177/1084713810375249.

Bierer, J.A., Faulkner, K.F. (2010). Identifying cochlear implant channels with poor electrode-neuron interface: partial tripolar, single-channel thresholds and psychophysical tuning curves. *Ear Hear*. 31(2), 247-258. doi:10.1097/AUD.0b013e3181c7daf4.

Bierer, J.A., Middlebrooks, J.C. (2002). Auditory cortical images of cochlear-implant stimuli: dependence on electrode configuration. *J Neurophysiol*. 87(1), 478-492. doi:10.1152/jn.00212.2001.

Bo, D., Huang, Y., Wang, B., Lu, P., Chen, W.X., Xu, Z.M. (2022). Auditory and Speech Outcomes of Cochlear Implantation in Children With Auditory Neuropathy Spectrum Disorder: A Systematic Review and Meta-Analysis. *Ann Otol Rhinol Laryngol*, 34894221092201. doi:10.1177/00034894221092201.

Budenz, C.L., Telian, S.A., Arnedt, C., Starr, K., Arts, H.A., El-Kashlan, H.K., Zwolan, T.A. (2013). Outcomes of cochlear implantation in children with isolated auditory neuropathy versus cochlear hearing loss. *Otol Neurotol*. 34(3), 477-483. doi:10.1097/MAO.0b013e3182877741.

Button, K.S., Ioannidis, J.P., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S., Munafò, M.R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci*. 14(5), 365-376. doi:10.1038/nrn3475.

Ching, T.Y., Day, J., Dillon, H., Gardner-Berry, K., Hou, S., Seeto, M., Wong, A., Zhang, V. (2013a). Impact of the presence of auditory neuropathy spectrum disorder (ANSD) on outcomes of children at three years of age. *Int J Audiol*. 52 Suppl 2(0 2), S55-64. doi:10.3109/14992027.2013.796532.

Ching, T.Y., Dillon, H., Marnane, V., Hou, S., Day, J., Seeto, M., Crowe, K., Street, L., Thomson, J., Van Buynder, P., Zhang, V., Wong, A., Burns, L., Flynn, C., Cupples, L., Cowan, R.S., Leigh, G., Sjahalam-King, J., Yeh, A. (2013b). Outcomes of early- and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear Hear*. 34(5), 535-552. doi:10.1097/AUD.0b013e3182857718.

Fitzpatrick, E.M., Johnson, E., Durieux-Smith, A. (2011). Exploring factors that affect the age of cochlear implantation in children. *Int J Pediatr Otorhinolaryngol*. 75(9), 1082-1087. doi:10.1016/j.ijporl.2011.05.018.

Harrison, M., Roush, J. (1996). Age of suspicion, identification, and intervention for infants and young children with hearing loss: a national study. *Ear Hear*. 17(1), 55-62. doi:10.1097/00003446-199602000-00007.

Humphriss, R., Hall, A., Maddocks, J., Macleod, J., Sawaya, K., Midgley, E. (2013). Does cochlear implantation improve speech recognition in children with auditory neuropathy spectrum disorder? A systematic review. *Int J Audiol*. 52(7), 442-454. doi:10.3109/14992027.2013.786190.

Jafari, Z., Malayeri, S., Ashayeri, H. (2007). The ages of suspicion, diagnosis, amplification, and intervention in deaf children. *Int J Pediatr Otorhinolaryngol*. 71(1), 35-40. doi:10.1016/j.ijporl.2006.08.014.

James, A.L., Osborn, H.A., Osman, H., Papaioannou, V., Gordon, K.A. (2020). The limitation of risk factors as a means of prognostication in auditory neuropathy spectrum disorder of perinatal onset. *Int J Pediatr Otorhinolaryngol*. 135, 110112. doi:10.1016/j.ijporl.2020.110112.

Kittrell, A.P., Arjmand, E.M. (1997). The age of diagnosis of sensorineural hearing impairment in children. *Int J Pediatr Otorhinolaryngol*. 40(2-3), 97-106. doi:10.1016/s0165-5876(97)01506-1.

Kontorinis, G., Lloyd, S.K., Henderson, L., Jayewardene-Aston, D., Milward, K., Bruce, I.A., O'Driscoll, M., Green, K., Freeman, S.R. (2014). Cochlear implantation in children with

auditory neuropathy spectrum disorders. *Cochlear Implants Int*. 15 Suppl 1, S51-54. doi:10.1179/1467010014z.000000000157.

Kral, A., Dorman, M.F., Wilson, B.S. (2019). Neuronal Development of Hearing and Language: Cochlear Implants and Critical Periods. *Annu Rev Neurosci*. 42, 47-65. doi:10.1146/annurev-neuro-080317-061513.

Kral, A., Sharma, A. (2012). Developmental neuroplasticity after cochlear implantation. *Trends Neurosci*. 35(2), 111-122. doi:10.1016/j.tins.2011.09.004.

le Roux, T., Vinck, B., Butler, I., Cass, N., Louw, L., Nauta, L., Schlesinger, D., Soer, M., Tshifularo, M., Swanepoel de, W. (2016). Predictors of pediatric cochlear implantation outcomes in South Africa. *Int J Pediatr Otorhinolaryngol*. 84, 61-70. doi:10.1016/j.ijporl.2016.02.025.

Myers, K., Nicholson, N. (2021). Cochlear Implant Behavioral Outcomes for Children With Auditory Neuropathy Spectrum Disorder: A Mini-Systematic Review. *Am J Audiol*. 30(3), 777-789. doi:10.1044/2021_aja-20-00175.

Omar, M., Qatanani, A.M., Douglas, N.O., Nawash, B.S., Ibrahim, T., Kaleem, S.Z., McKinnon, B.J. (2022). Sociodemographic disparities in pediatric cochlear implantation outcomes: A systematic review. *Am J Otolaryngol*. 43(5), 103608. doi:10.1016/j.amjoto.2022.103608.

Ozcebe, E., Sevinc, S., Belgin, E. (2005). The ages of suspicion, identification, amplification and intervention in children with hearing loss. *Int J Pediatr Otorhinolaryngol*. 69(8), 1081-1087. doi:10.1016/j.ijporl.2005.03.002.

Peng, K.A., Kuan, E.C., Hagan, S., Wilkinson, E.P., Miller, M.E. (2017). Cochlear Nerve Aplasia and Hypoplasia: Predictors of Cochlear Implant Success. *Otolaryngol Head Neck Surg*. 157(3), 392-400. doi:10.1177/0194599817718798.

Pfingst, B.E., Burkholder-Juhasz, R.A., Zwolan, T.A., Xu, L. (2008). Psychophysical assessment of stimulation sites in auditory prosthesis electrode arrays. *Hear Res*. 242(1-2), 172-183. doi:10.1016/j.heares.2007.11.007.

Prendergast, S.G., Lartz, M.N., Fiedler, B.C. (2002). Ages of diagnosis, amplification, and early intervention of infants and young children with hearing loss: findings from parent interviews. *Am Ann Deaf*. 147(1), 24-30. doi:10.1353/aad.2012.0198.

Rance, G., Starr, A. (2015). Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. *Brain*. 138(Pt 11), 3141-3158. doi:10.1093/brain/awv270.

Riggs, W.J., Roche, J.P., Giardina, C.K., Harris, M.S., Bastian, Z.J., Fontenot, T.E., Buchman, C.A., Brown, K.D., Adunka, O.F., Fitzpatrick, D.C. (2017). Intraoperative Electrocochleographic Characteristics of Auditory Neuropathy Spectrum Disorder in Cochlear Implant Subjects. *Front Neurosci*. 11, 416. doi:10.3389/fnins.2017.00416.

Saidia, A.R., Ruel, J., Bahloul, A., Chaix, B., Venail, F., Wang, J. (2023). Current Advances in Gene Therapies of Genetic Auditory Neuropathy Spectrum Disorder. *J Clin Med*. 12(3). doi:10.3390/jcm12030738.

Sharma, A., Campbell, J. (2011). A sensitive period for cochlear implantation in deaf children. *J Matern Fetal Neonatal Med*. 24 Suppl 1(0 1), 151-153. doi:10.3109/14767058.2011.607614.

Snyder, R.L., Middlebrooks, J.C., Bonham, B.H. (2008). Cochlear implant electrode configuration effects on activation threshold and tonotopic selectivity. *Hear Res*. 235(1-2), 23-38. doi:10.1016/j.heares.2007.09.013.

Turner, R.M., Bird, S.M., Higgins, J.P. (2013). The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLoS One*. 8(3), e59202. doi:10.1371/journal.pone.0059202.

Vesseur, A., Free, R., Snels, C., Dekker, F., Mylanus, E., Verbist, B., Frijns, J. (2018). Hearing Restoration in Cochlear Nerve Deficiency: the Choice Between Cochlear Implant or Auditory Brainstem Implant, a Meta-analysis. *Otol Neurotol*. 39(4), 428-437. doi:10.1097/mao.0000000000001727.

Walker, E., McCreery, R., Spratford, M., Roush, P. (2016). Children with Auditory Neuropathy Spectrum Disorder Fitted with Hearing Aids Applying the American Academy of Audiology Pediatric Amplification Guideline: Current Practice and Outcomes. *J Am Acad Audiol*. 27(3), 204-218. doi:10.3766/jaaa.15050.

Wolfe, J., 2020. Cochlear Implants: Audiologic Management and Considerations for Implantable Hearing Devices. Plural Publishing Inc., San Diego.

Yoshinaga-Itano, C., Sedey, A.L., Coulter, D.K., Mehl, A.L. (1998). Language of early- and later-identified children with hearing loss. *Pediatrics*. 102(5), 1161-1171. doi:10.1542/peds.102.5.1161.

Appendices

Appendix I (Chapter 2): CHEO REB Letter of Approval

Whittingham, JoAnne

From:
Sent: Friday, October 28, 2022 9:22 AM
To: Lessard, Chantal
Cc: Sokalski, Ashley; Whittingham, JoAnne; Anderson, Natalie
Subject: REB Protocol No 22/83X - Final Approval - Delegated Review

EXTERNAL MAIL*

CHEO

CHEO REB
Letter of Approval

REB Protocol No: 22/83X
ROMEO File No: 20221267
Principal Investigator: Dr. Chantal Lessard
Protocol Title: CHEOREB# 22/83X - Predictors of Amplification Outcomes in Children with Auditory Neuropathy Spectrum Disorders (ANSD)

Protocol Status: Active

Approval Date: October 28, 2022
Approval Expiry Date: October 15, 2023

The CHEO REB has conducted a delegated review and determined that the conditions of approval have been satisfied for the above-named study. Approval is valid for the period indicated above. This research study is to be conducted by the investigator noted above. Annual renewals or study closures must be completed before the expiry date noted above.

REB members involved in the study do not participate in the review, deliberations, or decision.

Documents Approved:

Document Name	Comments	Version Date
Case Report Form	Case report form (variable list)	2022/10/12
Protocol	Protocol Version 4	2022/10/12

Any modifications made to the study must be reviewed and approved by the REB prior to implementation, except when necessary to eliminate immediate danger or hazard(s) to study participants or when the change(s) involves administrative aspects of the study. Investigators must promptly alert the REB of any changes that increase the risk to participants or affect the safety of participants, all unanticipated and harmful events that occur, and new information that significantly impact the conduct of the study.

The CHEO REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans (TCPS 2); the International Conference on

Harmonization Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; and Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The CHEO REB is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact the Research Ethics Office if you have any questions.

Best wishes for the successful conduct of your research.

Cécile Bensimon, MA, PhD
Chair, Research Ethics Board
Présidente, Comité d'éthique de la recherche

Appendix II (Chapter 2): University of Ottawa Ethical Approval

18/11/2022

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Lettre d'approbation administrative | Letter of administrative approval

Numéro de dossier / Ethics File Number	H-11-22-8149
Titre du projet / Project Title	Predictors of Amplification Outcomes in Children with Auditory Neuropathy Spectrum Disorders (ANSD)
Type de projet / Project Type	Recherche de professeur / Professor's research project
CÉR primaire / Primary REB	
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	18/11/2022
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	16/10/2023

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Amineh KORAVAND	École des sciences de la réadaptation / School of Rehabilitation Sciences	Chercheur Principal / Principal Investigator
Zahra JAFARI	École des sciences de la réadaptation / School of Rehabilitation Sciences	Co-chercheur principal / Co-principal investigator
Chantal LESSARD	CHEO	Co-chercheur / Co-investigator
Ashley SOKALSKI	CHEO	Coordonnateur de recherche / Research Coordinator
Jennifer Ti NGUYEN	École des sciences de la réadaptation / School of Rehabilitation Sciences	Assistant de recherche / Research Assistant

Conditions spéciales ou commentaires / Special conditions or comments:

CHEO REB Protocol No: 22/83X

550, rue Cumberland, pièce 154 550 Cumberland Street, Room 154
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada

613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

18/11/2022

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

L'Université d'Ottawa a signé une Entente, conforme aux exigences de la plus récente version de l'EPTC et tout autre règlement ou législation applicable, permettant au CÉR ci-haut nommé d'être désigné comme CÉR primaire pour les projets de recherche où

1) les activités principales de recherche sont menées sous l'autorité ou sous les auspices de l'établissement lié au CÉR primaire et

2) Une partie du projet est également réalisé sous l'autorité ou sous les auspices de l'Université d'Ottawa.

Cette lettre confirme que l'Université d'Ottawa a autorisé que le CÉR primaire soit le CÉR officiel pour l'évaluation et la supervision de ce projet de recherche. Ceci n'est pas une approbation éthique.

Afin de nous aider à garder votre dossier à jour, veuillez soumettre une copie de toutes demandes de modification, renouvellement d'approbation éthique etc. soumis à et approuvé par le CÉR primaire dès qu'elles sont disponibles.

Cette approbation administrative est valide pour la durée indiquée ci-haut et est sujette aux conditions énumérées dans la section intitulée « Conditions spéciales ou commentaires ».

The University of Ottawa has signed an Agreement, compliant with current TCPS guidelines and any other applicable guidelines or legislation regarding multisite review, allowing the REB named above to serve as Board of Record (BoR) for research projects where

1) the main research activities are conducted within the auspices or jurisdiction of the BoR's institution and

2) parts of the project are also conducted under the jurisdiction or auspices of the University of Ottawa.

This letter confirms that the University of Ottawa has authorized the REB named above to serve as Board of Record for the review and oversight of this research project. This is not an REB approval.

In order to help us keep your file up to date, please submit a copy of all amendment requests, project renewals or any other changes submitted to and approved by the BoR, as they become available.

Administrative approval is valid for the period indicated above and is subject to the conditions listed in the section entitled «Special conditions or comments».

Catherine PAQUET
Directeur / Director
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

550, rue Cumberland, pièce 154 550 Cumberland Street, Room 154
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada

613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

Appendix III (Chapter 2): supplemental data analysis

Figure 1

It is noteworthy that after removing a few outliers (i.e., data points over ±2SD) in Figure 1 (page 62), the reported relationships remained significant. Figure 1A: r = -0.752, p = 0.001, n = 13; Figure 1B: r = -0.530, p = 0.035, n = 19; Figure 1C: r = -0.613, p = 0.041, n = 12; Figure 1D: no outlier was identified.)

Table 5

Table 5 (page 70) outlines the results of a Forward Linear Multiple Regression Model aimed at identifying variables with prognostic value for intervention outcomes. The included variables in the model were age at HL diagnosis, age at HA fitting, age at CI activation, length of follow-up with CI/HA, onset of HL, use of bilateral amplification, history of NICU admission, preterm birth, ADs/MCs, and sex.

To ensure the appropriateness of the statistical test and the number of variables included in the model, the same analyses were conducted using a Stepwise Linear Multiple Regression Model, as well as by considering only the four variables that exhibited a statistically significant association with speech perception outcomes (i.e., age at HL diagnosis, age at HA fitting, age at CI activation, and length of follow-up with CI/HA). The results of the Forward Linear Multiple Regression Model and the Stepwise Linear Multiple Regression Model, including 10 or 4 variables, were quite similar, providing further confidence in the reported analyses.

Appendix IV (Chapter 3): PRISMA 2020 Checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix V (Chapter 3): Crowe Critical Appraisal Tool (CCAT)

Crowe Critical Appraisal Tool (CCAT) Form (v1.4) Reference Reviewer

This form must be used in conjunction with the CCAT User Guide (v1.4); otherwise validity and reliability may be severely compromised.

Citation

	Year

Research design (add if not listed)

❑ Not research	Article | Editorial | Report | Opinion | Guideline | Pamphlet | ...	
❑ Historical	...	
❑ Qualitative	Narrative | Phenomenology | Ethnography | Grounded theory | Narrative case study | ...	
❑ Descriptive, Exploratory, Observational	A. Cross-sectional | Longitudinal | Retrospective | Prospective | Correlational | Predictive | ...	
	B. Cohort | Case-control | Survey | Developmental | Normative | Case study | ...	
Experimental	❑ True experiment	Pre-test/post-test control group | Solomon four-group | Post-test only control group | Randomised two-factor | Placebo controlled trial | ...
	❑ Quasi-experiment	Post-test only | Non-equivalent control group | Counter balanced *(cross-over)* | Multiple time series | Separate sample pre-test post-test [no Control] [Control] | ...
	❑ Single system	One-shot experimental *(case study)* | Simple time series | One group pre-test/post-test | Interactive | Multiple baseline | Within subjects *(Equivalent time, repeated measures, multiple treatment)* | ...
❑ Mixed Methods	Action research | Sequential | Concurrent | Transformative | ...	
❑ Synthesis	Systematic review | Critical review | Thematic synthesis | Meta-ethnography | Narrative synthesis | ...	
❑ Other	...	

Variables and analysis

Intervention(s), Treatment(s), Exposure(s)	Outcome(s), Output(s), Predictor(s), Measure(s)	Data analysis method(s)

Sampling

Total size		Group 1		Group 2		Group 3		Group 4		Control	
Population, sample, setting											

Data collection (add if not listed)

Audit/Review	a) Primary | Secondary | ... b) Authoritative | Partisan | Antagonist | ... c) Literature | Systematic | ...	Interview	a) Formal | Informal | ... b) Structured | Semi-structured | Unstructured | ... c) One-on-one | Group | Multiple | Self-administered | ...
Observation	a) Participant | Non-participant | ... b) Structured | Semi-structured | Unstructured | ... c) Covert | Candid | ...	Testing	a) Standardised | Norm-ref | Criterion-ref | Ipsative | ... b) Objective | Subjective | ... c) One-on-one | Group | Self-administered | ...

Scores

Preliminaries		Design		Data Collection		Results		Total [/40]	
Introduction		Sampling		Ethical Matters		Discussion		Total [%]	

General notes

Category Item	Item descriptors [☑ Present; ☒ Absent; ■ Not applicable]	Description [Important information for each item]	Score [0–5]
1. Preliminaries			
Title	1. Includes study aims ❑ and design ❑		
Abstract (assess last)	1. Key information ❑ 2. Balanced ❑ and informative ❑		
Text (assess last)	1. Sufficient detail others could reproduce ❑ 2. Clear/concise writing ❑, table(s) ❑, diagram(s) ❑, figure(s) ❑		
		Preliminaries [/5]	
2. Introduction			
Background	1. Summary of current knowledge ❑ 2. Specific problem(s) addressed ❑ and reason(s) for addressing ❑		
Objective	1. Primary objective(s), hypothesis(es), or aim(s) ❑ 2. Secondary question(s) ❑		
	Is it worth continuing?	**Introduction [/5]**	
3. Design			
Research design	1. Research design(s) chosen ❑ and why ❑ 2. Suitability of research design(s) ❑		
Intervention, Treatment, Exposure	1. Intervention(s)/treatment(s)/exposure(s) chosen ❑ and why ❑ 2. Precise details of the intervention(s)/treatment(s)/exposure(s) ❑ for each group ❑ 3. Intervention(s)/treatment(s)/exposure(s) valid ❑ and reliable ❑		
Outcome, Output, Predictor, Measure	1. Outcome(s)/output(s)/predictor(s)/measure(s) chosen ❑ and why ❑ 2. Clearly define outcome(s)/output(s)/predictor(s)/measure(s) ❑ 3. Outcome(s)/output(s)/predictor(s)/measure(s) valid ❑ and reliable ❑		
Bias, etc	1. Potential bias ❑, confounding variables ❑, effect modifiers ❑, interactions ❑ 2. Sequence generation ❑, group allocation ❑, group balance ❑, and by whom ❑ 3. Equivalent treatment of participants/cases/groups ❑		
	Is it worth continuing?	**Design [/5]**	
4. Sampling			
Sampling method	1. Sampling method(s) chosen ❑ and why ❑ 2. Suitability of sampling method ❑		
Sample size	1. Sample size ❑, how chosen ❑, and why ❑ 2. Suitability of sample size ❑		
Sampling protocol	1. Target/actual/sample population(s): description ❑ and suitability ❑ 2. Participants/cases/groups: inclusion ❑ and exclusion ❑ criteria 3. Recruitment of participants/cases/groups ❑		
	Is it worth continuing?	**Sampling [/5]**	
5. Data collection			
Collection method	1. Collection method(s) chosen ❑ and why ❑ 2. Suitability of collection method(s) ❑		
Collection protocol	1. Include date(s) ❑, location(s) ❑, setting(s) ❑, personnel ❑, materials ❑, processes ❑ 2. Method(s) to ensure/enhance quality of measurement/instrumentation ❑ 3. Manage non-participation ❑, withdrawal ❑, incomplete/lost data ❑		
	Is it worth continuing?	**Data collection [/5]**	
6. Ethical matters			
Participant ethics	1. Informed consent ❑, equity ❑ 2. Privacy ❑, confidentiality/anonymity ❑		
Researcher ethics	1. Ethical approval ❑, funding ❑, conflict(s) of interest ❑ 2. Subjectivities ❑, relationship(s) with participants/cases ❑		
	Is it worth continuing?	**Ethical matters [/5]**	
7. Results			
Analysis, Integration, Interpretation method	1. A.I.I. method(s) for primary outcome(s)/output(s)/predictor(s) chosen ❑ and why ❑ 2. Additional A.I.I. methods (e.g. subgroup analysis) chosen ❑ and why ❑ 3. Suitability of analysis/integration/interpretation method(s) ❑		
Essential analysis	1. Flow of participants/cases/groups through each stage of research ❑ 2. Demographic and other characteristics of participants/cases/groups ❑ 3. Analyse raw data ❑, response rate ❑, non-participation/withdrawal/incomplete/lost data ❑		
Outcome, Output, Predictor analysis	1. Summary of results ❑ and precision ❑ for each outcome/output/predictor/measure 2. Consideration of benefits/harms ❑, unexpected results ❑, problems/failures ❑ 3. Description of outlying data (e.g. diverse cases, adverse effects, minor themes) ❑		
		Results [/5]	
8. Discussion			
Interpretation	1. Interpretation of results in the context of current evidence ❑ and objectives ❑ 2. Draw inferences consistent with the strength of the data ❑ 3. Consideration of alternative explanations for observed results ❑ 4. Account for bias ❑, confounding/effect modifiers/interactions/imprecision ❑		
Generalisation	1. Consideration of overall practical usefulness of the study ❑ 2. Description of generalisability (external validity) of the study ❑		
Concluding remarks	1. Highlight study's particular strengths ❑ 2. Suggest steps that may improve future results (e.g. limitations) ❑ 3. Suggest further studies ❑		
		Discussion [/5]	
9. Total			
Total score	1. Add all scores for categories 1–8		
		Total [/40]	

Appendix VI (Chapter 4): AMSTAR-2

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☐ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☐ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☐ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☐ Yes
☐ No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☐ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:
- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☐ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from
- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:
- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes
- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☐ No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs
For Yes:
- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☐ No meta-analysis conducted

For NRSI
For Yes:
- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:
- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:
- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:
- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:
- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix VII (Chapter 4): ROBIS: Tool to Assess Risk of Bias in Systematic Reviews

Phase 1: Assessing relevance (Optional)

ROBIS is designed to assess the risk of bias in reviews with questions relating to interventions, aetiology, diagnosis and prognosis. State your overview/guideline question (target question) and the question being addressed in the review being assessed:

Intervention reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Intervention(s):		
Comparator(s):		
Outcome(s):		

For aetiology reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Exposure(s) and comparator(s):		
Outcome(s):		

For DTA reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients):		
Index test(s):		
Reference standard:		
Target condition:		

For prognostic reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients:		
Outcome to be predicted:		
Intended use of model:		
Intended moment in time:		

Does the question addressed by the review match the target question?	YES/NO/UNCLEAR

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings Rationale for concern:	LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding methods used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review Rationale for risk:	RISK: LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION