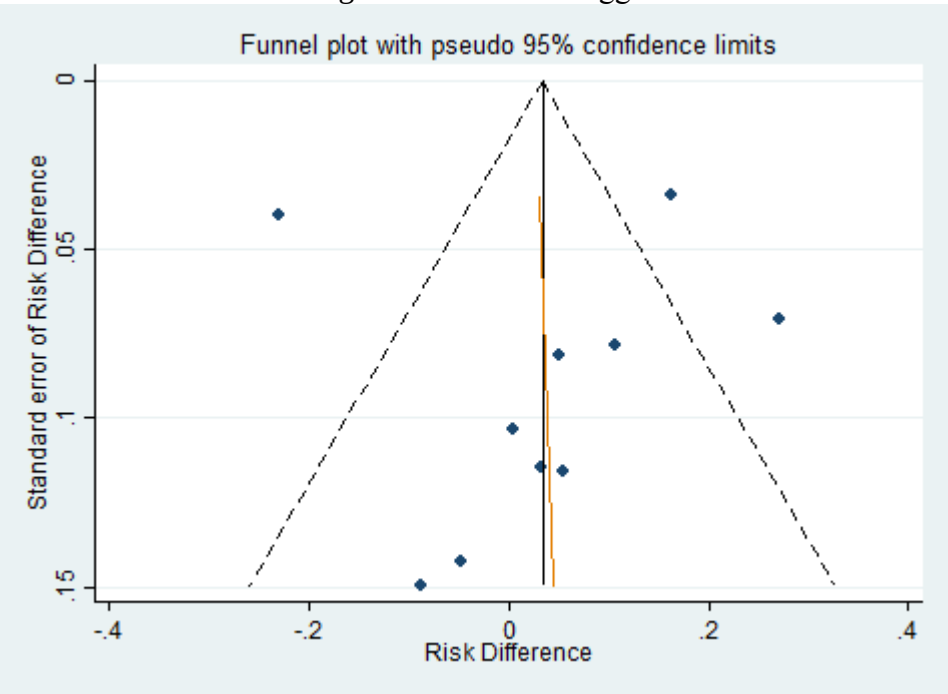
Appendices (all available online only)

Appendix 1.

The 15% cut-off to include predominantly non-syndromic, unexplained hearing loss was set at this value according to the following reasoning: In a worst case scenario (i.e. maximum skew from inclusion of syndromic patients), a syndromic population might have a 100% anomaly risk. In that scenario, "dilution" of the nonsyndromic population will increase the proportion estimated by $\leq$0.1 if syndromic proportion is <15% of the study population (See Table below). The 0.3 value was selected from preliminary data suggesting a potential 30% diagnostic yield, at the outset of the reported analysis.

Proportion of SNHL w anomaly (estimate)		**Proportion of study population**		**Estimated reported proportion**
Nonsyndromic	Syndromic	Nonsyndromic	Syndromic	Nonsyndromic+syndromic
0.3	1	1	0	0.3
0.3	1	0.95	0.05	0.335
0.3	1	0.9	0.1	0.37
0.3	1	0.85	0.15	0.405
0.3	1	0.8	0.2	0.44
0.3	1	0.75	0.25	0.475
0.3	1	0.7	0.3	0.51
0.3	1	0.65	0.35	0.545
0.3	1	0.6	0.4	0.58
0.3	1	0.55	0.45	0.615
0.3	1	0.5	0.5	0.65
0.3	1	0.45	0.55	0.685
0.3	1	0.4	0.6	0.72
0.3	1	0.35	0.65	0.755
0.3	1	0.3	0.7	0.79
0.3	1	0.25	0.75	0.825
0.3	1	0.2	0.8	0.86
0.3	1	0.15	0.85	0.895
0.3	1	0.1	0.9	0.93
0.3	1	0.05	0.95	0.965
0.3	1	0	1	1

Appendix 2. Funnel plot to assess for publication bias. Egger's test showed no significant evidence of publication bias (p=0.955). The tan line shows the fitted regression line from Egger's test.



Appendix 3A. Brain Findings in MRI of Children with Hearing Loss of Unknown Etiology

Author, year	Study design (Level)	Percent (Proportion) with MRI-Identified Diagnoses	Age Group	Extent of Hearing Loss in the Study Population	Additional Comments
Lin, 2011[83]	Retrospective case series with chart review	24% (58/242) of patients had brain anomalies	"Children" Specific ages NR	Severe to profound SNHL	Consecutive
Jonas, 2012[50]	Retrospective case series with chart review of cochlear implant candidates	30% (49/162) of patients had brain anomalies (51 anomalies total).	Mean age at scan 3 years 8 months	Severe/profound bilateral SNHL	Consecutive
Trimble, 2007[57]	Retrospective case series with chart review of CI candidates	37% (34/92) of patients	7 months-17 years (mean: 4.7 years)	Profound HL	Consecutive
McClay, 2008[27]	Retrospective case series with chart review of children with unilateral or bilateral SNHL	20% (33/166) of patients had intracranial anomalies	1 mo – 17 years (mean 5.3 years)	Bilateral SNHL, 59% (101/170) Unilateral SNHL, 41% (69/170) Among ears, types of SNHL: Mild, 11% (29/271) Moderate, 19% (51/271) Severe, 10% (28/271) Profound, 41% (110/271) Progressive, 3% (8/271) Sloping, 1% (4/271) Sudden, 1% (3/271) Fluctuating, 1% (4/271) High-frequency, 1% (4/271) Unknown, 11% (30/271)	Consecutive
Hong, 2010[52]	Retrospective case series with chart review of cochlear implant recipients	18% (10/57) of patients had incidental brain findings	12-194 months (mean 58 months)	Severe/profound bilateral SNHL	Consecutive Follow up time greater than 6 months
Parry, 2005[5]	Retrospective case series with chart review of cochlear implant candidates	30% (17/56) of patients had brain anomalies	NR "pediatric"	Severe/profound bilateral SNHL	Consecutive
Lapointe, 2005[46]	Retrospective case series with chart review of patients evaluated for cochlear implantation	20% (8/40) of patients showed significant brain abnormalities	"Children" Ages NR	Profound bilateral SNHL	Consecutive
Kimani, 2010[48]	Retrospective case series with chart review of children with SNHL	33% (29/87) of patients without CMV had brain anomalies	1 – 5 years	Profound HL, 46% (43/101) Severe HL, (15/101) Bilateral HL, 85% (87/101)	All children referred from newborn screening. Consecutive status of patients NR.

HL – Hearing loss; SNHL – Sensorineuronal hearing loss; NR – Not reported; CMV – cytomegalovirus.

Tarshish, 2013 identified 1 patient with brain findings suggestive of CMV. In Kimani, the 87 brain scans denominator reflects the 97 patients without the 10 patients with known CMV.

Appendix 3A. Brain Findings in MRI of Children with Hearing Loss of Unknown Etiology (continued)

Author, year	Study design (Level)	Percent (Proportion) with MRI-Identified Diagnoses	Age Group	Extent of Hearing Loss in the Study Population	Additional Comments
Haffey, 2013[42]	Retrospective case series of patients with unilateral SNHL	13% (4/31) of patients had brain anomalies	0-17 years old (mean: 5.6 years)	Type of hearing loss: Low frequency, 1% (1/79) Mid-frequency, 22% (17/79) High frequency, 37% (29/79) Flat, 41% (32/79)	Consecutive Follow up time of 5 years.
Mafong, 2002[38]	Retrospective case series with chart review of children with SNHL	19% (4/21) of patients had brain anomalies	1-18 years (mean 9 years)	Bilateral SNHL, 83% (95/114) Unilateral SNHL, 11% (13/114). Moderate to profound hearing loss, 81% (92/114) Mild hearing loss, 19% (22/114)	Consecutive
Simons, 2006[8]	Retrospective case series with chart review of children with unilateral or bilateral asymmetric HL	10% (5/50) of patients had brain anomalies	0-17 years	Unilateral SNHL, 80% (40/50) Asymmetric SNHL, 20% (10/50)	Consecutive
Russo, 2006[45]	Retrospective case series with chart review of children with profound SNHL	0% (0/17) of patients had brain anomalies	Median age 3 (range <1-14 years old)	Profound hearing loss	Consecutive. Subgroup analysis of profound SNHL of unknown etiology. (CMV, meningitis, rubella, syphilis excluded). Sagittal high-resolution temporal bone MRI.
Brookhouser, 1991[49]	Retrospective case series with chart review of patients with unilateral SNHL	0% (0/7) of patients had brain anomalies	0-19.8 years (mean 8.8 years)	Borderline 19% (12/64) Mild 31% (20/64) Moderate 25% (16/64) Severe 42% (27/64) Profound 19% (12/64) Anacusic 26% (17/64) High-frequency 3% (2/64)	Consecutive Follow-up data available for periods of 1-15 years. Brain findings described as “no space occupying lesions”.
Ohlms, 1999[39]	Retrospective case series with chart review of children with SNHL or mixed HL	0% (0/6) of patients had a brain anomaly that seemed related to the hearing loss	0 - 10 years at diagnosis (mean 2 years)	For the entire study, 81% (92/114) had severe or profound HL (includes sample without imaging data)	Consecutive status of patients NR

Appendix 3B. Counts and Types of Brain Anomalies in Children in Studies of MRI of Children with Hearing Loss

Author, year	Jonas, 2012[50]	Hong, 2010[52]	Parry, 2005[5]	Lapointe, 2005[46]	Kimani, 2010[48]	Simons, 2006[8]	Haffey, 2013[42]	Mafong, 2002[38]	Trimble, 2007[57]	Lin, 2011[83]	McClay, 2008[27]
Malignant/Neoplastic Masses	10% (5/51)	--	--	--	--	--	--	--	--	--	9% (3/33)
Non-malignant/ Non-neoplastic Masses	4% (2/51)	--	--	--	--	13% (2/15)	10% (1/10)	14% (1/7)	9% (3/34)	--	--
Vascular Lesions	4% (2/51)	--	--	--	--	--	10% (1/10)	--	--	--	--
Anatomic/Structural Findings	12% (6/51)	--	18% (3/17)	38% (3/8)	21% (6/29)	20% (3/15)	10% (1/10)	43% (3/7)	3% (1/34)	43% (5/58)	42% (14/33)
White Matter Findings	70% (36/51)	100% (10/10)	41% (8/17)	38% (3/8)	45% (13/29)	--	10% (1/10)	--	15% (5/34)	33% (19/58)	--
Grey Matter Findings	4% (2/51)	10% (1/10)	--	--	--	--	--	--	--	--	--
Cerebellar Findings	4% (2/51)	--	6% (1/17)	--		--	--	--	3% (1/34)	--	--
Ventricle/Cerebrospinal Fluid Finding			6% (1/17)	--	35% (10/29)	--	--	--	24% (8/34)	--	--
Heterotopia/ Dysplasia/ Encephalomalacia	4% (2/51)	--	--	38% (3/8)	--	--	--	--	3% (1/34)	31% (18/58)	--
Metabolic/Reactive/ Infectious Findings	2% (1/51)	20% (2/10)	53% (9/17)	--	--	--	--	--	44% (15/34)	28% (16/58)	33% (11/33)

Tarshish, 2013 identified 1 patient with brain findings suggestive of CMV. Ohlms, 1999; Brookhouser, 1991; and Russo, 2006 identified no patients with brain findings.

The denominators shown are the number of patients with non-normal MRI findings, except in Jonas, which reflect the total number of anomalies (not the total number of patients with anomalies).

Malignant /Neoplastics Masses includes: neoplasms, malignancies, unspecified "tumor." Non-malignant/Non-neoplastic Masses includes: cysts, lipoma, glioma. Vascular Lesions includes: vasculitis, cavernoma, hematoma. Anatomic/Structural includes: holoprosencephaly, abnormal brainstem/brainstem hypoplasia, microcephaly, corpus callosum hypoplasia/dysgenesis, bilateral hemispheric volume loss, immature brain appearance, Dandy Walker malformation, Chiari I/II, prominent temporal horns, pachygyria, cortex dysplasia. White matter findings includes: generalized changes/signal changes, myelination problems, periventricular leukomalacia. Grey Matter findings includes: general gray matter changes. Cerebellar Findings includes: hypoplasia, dysplasia. Ventricle/Cerebrospinal Fluid includes: shunt, ventriculomegaly, extra-axial cerebrospinal fluid (CSF). Heterotopia/Cortical Dysplasia/ Encephalomalacia includes: periventricular nodular heterotopia, ectopia, dysplasia, cortical dysplasia, encephalomalacia. Metabolic/Reactive/Infectious Findings includes: neurometabolic processes, gliosis, cytomegalovirus.

Appendix 4A. MRI Findings in Children with Auditory Spectrum Neuropathy

Author, year	Study design (Level)	Percent (Proportion) with MRI-Identified Diagnoses	Age Group	Extent of Hearing Loss in the Study Population	Additional Comments
Huang, 2010[53]	Retrospective case series with chart review	34% (35/103) of patients (otological) 36% (37/103) of patients (brain)	11 weeks – 13.5 years (mean of 2.31 years)	Bilateral ANSD, 77% (79/103) Unilateral ANSD, 23% (24/103)	Consecutive
Roche, 2010[54]	Retrospective case series with chart review	64% (68/107) of patients ("at least one imaging abnormality) 40% (42/106) of patients (intracranial abnormalities)	Mean age at MRI: 2.34±2.37 years	Of entire study population: Bilateral ANSD, 76% (90/118) Unilateral ANSD, 24% (28/118)	Consecutive
Teagle, 2010[55]	Prospective case series with chart review	38% (18/48) of patients (otological and brain combined)	14-241 months (mean of 88 months)	Of entire study population: Bilateral ANSD, 88% (50/58) Unilateral ANSD and bilateral HL, 12% (8/58)	Consecutive
Laury, 2009[56]	Retrospective case series with chart review	100% (10/10) of patients (otological and brain)	0-9 years old (mean 3.4 years)	Profound SNHL, 80% (8/10) Moderate to severe SNHL, 20% (2/10)	Consecutive Follow up time of 1-7 years

Appendix 4B. Counts and Types of Anomalies in Brain MRI of Children with Hearing Loss due to Auditory Neuropathy

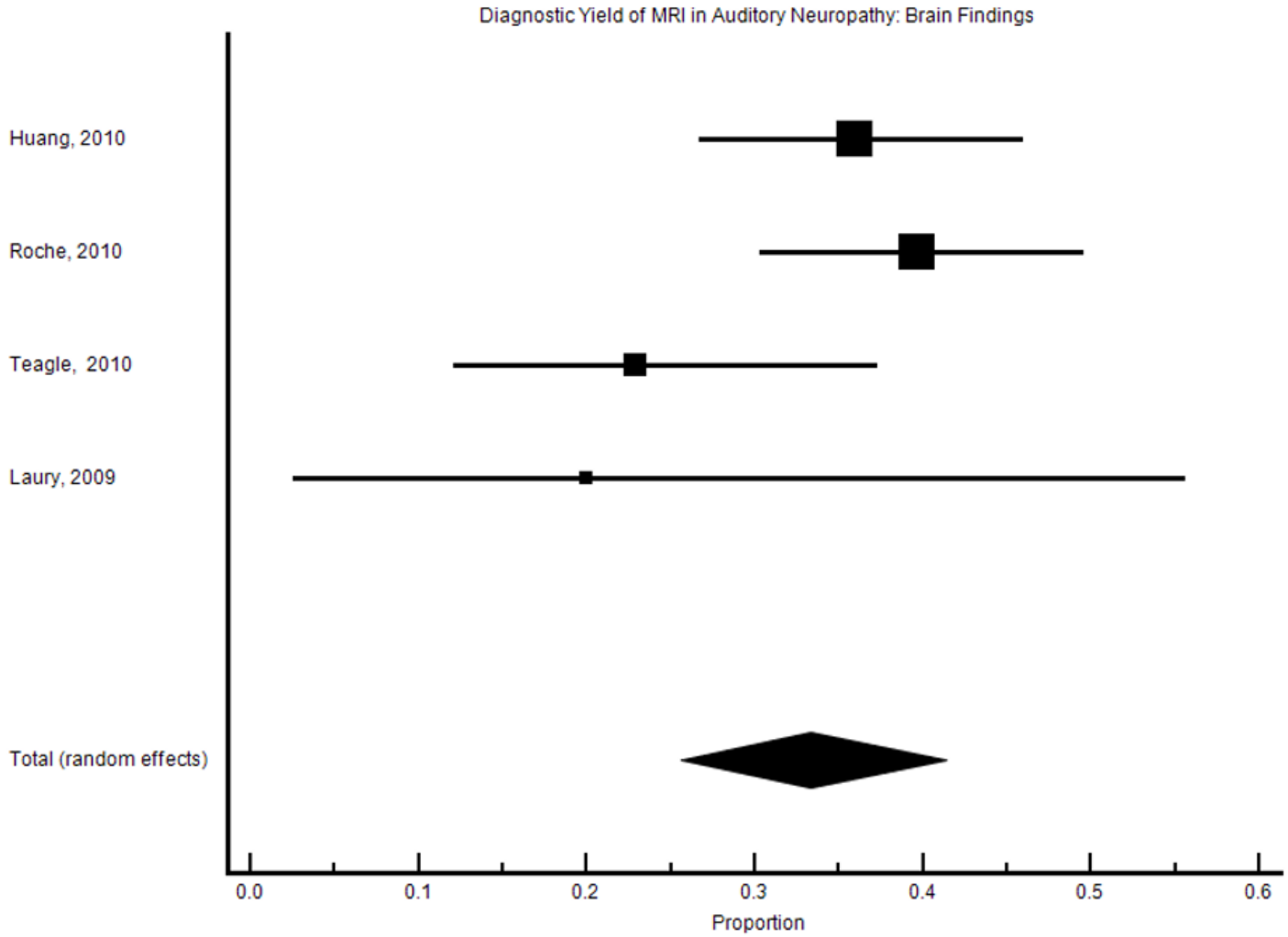
Author, year	Huang, 2010[53]	Teagle, 2010[55]	Laury, 2009[56]	Roche, 2010[54]
OTOLOGICAL	--	--	--	--
Cochlear malformation	31% (11/35)	17% (3/18)		16% (11/68)
Vestibular malformation	20% (7/35)	--		10% (7/68)
Large endolymphatic duct/sac	3% (1/35)	--	--	--
Cochlear nerve aplasia/absence/ dysplasia/ deficiency	97% (34/35)	50% (9/18)	80% (8/10)	53% (36/68)*
IAC stenosis/narrowing/atresia	34% (12/35)	--	20% (2/10) "Mildly narrow IAC"	27% (49/183 ears)
SCC malformation	17% (6/35)		--	9% (6/68)
Bony cochlear nerve canal stenosis/atresia	80% (28/35)	--	--	--
NEUROLOGICAL	--	--		--
Malignant/Neoplastic Masses	--	--	20% (2/10)	--
Non-malignant/ Non-neoplastic Masses	--	--	--	5% (2/42)
Dandy-Walker Malformation	--	11% (2/18)	--	10% (4/42)
Chiari Type I/II malformation	--	6% (1/18)	--	5% (2/42)
Other Anatomic/Structural Findings	Mid-/hindbrain malformation, 35% (13/37) Forebrain malformation, 19% (7/37)	Optoinfundibular dysplasia, 6% (1/18)	--	Microcephaly, 2% (1/42) Brainstem /cerebellum abnormality, 38% (16/42)** Cerebrum /midbrain abnormality, 17% (7/42
White Matter Findings	49% (18/37)	39% (7/18)		38% (16/42)
CNS myelination abnormality	--	--	--	7% (3/42)
Ventricle/Cerebrospinal Fluid Finding	51% (19/37)		--	Prominent temporal horns, 16% (33/212 temporal lobes) CSF and/or ventricle abnormalities, 48% (20/42)
Other Abnormalities	--	--	--	17% (7/42)***

White matter findings: generalized changes, myelination problems, periventricular leukomalacia
Non-malignant/ Non-neoplastic Masses: cerebellopontine angle arachnoid cyst, posterior fossa arachnoid cyst
*"Definite or possible cochlear nerve deficiency"
**Includes Dandy Walker and Chiari type I malformations
***Other abnormalities include: persistent hyperplastic primary vitreous, globe abnormality (n= 2), leptomeningeal enhancement, prominent perivascular spaces, and small optic nerve (n=2)

Appendix 4C. Heterogeneity Among Studies of Children with Auditory Neuropathy / Auditory Dyssynchrony, Proportion with Diagnostic Yield

Studies Included	Imaging Modality	Imaging Findings Included	Number of Studies in Group/Subgroup	I^2 (95% Confidence/ Uncertainty Interval)
All Studies	MRI	Both Otological and Brain Findings Quantified in Non-overlapping Patients	n=3	87% (63-95%)
All Studies	MRI	Otological Findings	n=3	81% (42-94%)
All Studies	MRI	Brain findings	n=4	40% (0-79%)

Appendix 4D. Forest plot of the diagnostic yield of MRI for brain anomalies in children with auditory neuropathy.



Appendix 5. Study Characteristics

Author, year	Prospective data collection	MRI method/ technique described	Diagnostic criteria described (e.g. size cut-off for EVA)	Masking of MRI assessors to clinical history or results of other imaging	Inter-rater Reliability/ Reproducibility described	Consecutive patients reported
Lin, 2011	--	--	x	--	--	x
Trimble, 2007	x	x	x	x	x	x
Kong, 2009	--	x	--	--	--	x
Declau, 2008	x	--	--	--	--	x
Komatsubara, 2007	--	x	--	--	--	--
Parry, 2005	--	x	x	--	--	x
Miyasaka, 2010	--	x	x	--	--	x
Simons, 2006	--	x	x	--	--	x
Preciado, 2004	--	--	--	--	--	x
Mafong, 2002	--	--	--	--	--	x
Ohlms, 1999	--	--	--	--	--	--
Tarshish, 2013	--	--	--	--	--	x
Ghogomu, 2013	x	--	--	--	--	x
Haffey, 2013	--	--	--	--	--	x
Young, 2012	--	x	x	x	--	x
Fahy, 2001	--	--	--	--	--	x
Russo, 2006	--	x	x	x	--	x
Lapointe, 2005	--	x	--	x	--	x
McClay, 2008	--	x	x	--	--	x
Clemmens, 2013	--	x	x	x	x	x
Kimani, 2010	--	x	--	x	--	--
Brookhouser, 1991	--	--	--	--	--	x
Whittemore, 2012	--	--	--	--	--	x
Jonas, 2012	--	x	--	--	--	x
Hong, 2010	--	x	--	--	--	x
Huang, 2010	--	x	x	x	--	x
Roche, 2010	--	x	x	--	--	x
Teagle, 2010	x	--	--	--	--	x
Laury, 2009	--	x	--	x	--	x

x: characteristic is present; --: characteristic is absent.