Visual and Hearing Impairments After Preterm Birth

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abstract

OBJECTIVES: Our aim was to determine and compare the incidences of sensory impairments among very preterm (VP) (<32 + 0/7 weeks), moderately preterm (MP) (32 + 0/7–33 + 6/7 weeks), late preterm (LP) (34 + 0/7–36 + 6/7 weeks), and term infants (≥37 weeks) and to establish risk factors of neurosensory disabilities.

METHODS: This national register study included all live-born infants in Finland between 1991 and 2008. Infants who died before the age of 1 year, who had any major congenital anomaly, or had missing data were excluded (n = 21 007; 2.0%). A total of 1 018 256 infants were analyzed. Incidences of hearing loss, visual disturbances or blindness, other ophthalmologic disorders, and retinopathy of prematurity were determined for gestational age (GA) groups. Risk factors of hearing loss and visual disturbances or blindness were analyzed.

RESULTS: The incidences of sensory impairments decreased with advancing GA at birth (P < .001). The most prominent factors associated with increased risks of hearing loss and visual impairment were intracranial hemorrhage and convulsions. VP (odds ratio [OR] 2.34; 95% confidence interval [CI] 1.75–3.14) and LP (OR 1.26; 95% CI 1.04–1.52) births were associated with an increased risk of hearing loss, and VP (OR 1.94; 95% CI 1.55–2.44), MP (OR 1.42; 95% CI 1.11–1.80), and LP (OR 1.31; 95% CI 1.16–1.49) births predicted an increased risk of visual impairment.

CONCLUSIONS: Incidences of sensory impairment decreased with increasing GA at birth. The most prominent risk factors predictive of sensory disabilities were intracranial hemorrhage and convulsions. VP and LP births were associated with an increased risk of hearing loss, and VP, MP, and LP births were associated with an increased risk of visual impairment.

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Dr Hirvonen conceptualized the study, drafted the initial manuscript, and participated in the analytic planning; Drs Ojala, Korhonen, Haataja, Eriksson, and Gissler participated in the analytic planning and critically reviewed and revised the manuscript; Ms Luukkaala conducted the statistical analyses and critically reviewed and revised the manuscript; Dr Tammela designed and supervised the study and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Very preterm birth is associated with an increased risk of sensory disabilities, and the risk increases with decreasing gestational age at birth. There are few reports concerning sensory impairment among moderately and late-preterm children.

WHAT THIS STUDY ADDS: The incidences of hearing loss and visual impairment were increased among moderately and late-preterm infants compared with term-born children. The most prominent risk factors predictive of these disabilities were convulsions during the neonatal period and intracranial hemorrhage.

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TABLE 1 Characteristics of the Mothers and the Infants Alive at 1 Year of Age Without Major Congenital Malformations (n = 1 018 256)

	VP <32 wk, n = 6329	MP 32 + 0/7–33 + 6/7 wk (n = 6796)	LP 34 + 0/7–36 + 6/7 wk, n = 39 928	Term or Postterm ≥37 wk, n = 965 203	P[a]	P[b]	P[c]	P[d]
Study periods, y, n (%)					.677	.084	.003	<.001
1991–1995	1780 (0.58)	1937 (0.63)	11 777 (3.82)	293 228 (95.0)				
1996–2001	2159 (0.66)	2269 (0.69)	13 361 (4.08)	309 889 (94.6)				
2002–2008	2390 (0.63)	2590 (0.68)	14 790 (3.87)	362 086 (94.8)				
Mothers								
Age, mean (SD)	30.2 (5.8)	29.8 (5.7)	29.7 (5.5)	29.2 (5.3)	<.001	<.001	<.001	<.001
Smoking, n (%)	1187 (18.8)	1184 (17.4)	6602 (16.5)	144 094 (14.9)	<.001	<.001	<.001	<.001
Primipara, n (%)	3314 (52.4)	3792 (55.8)	20 040 (50.2)	392 574 (40.7)	<.001	.001	<.001	<.001
Previous deliveries, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–2)	<.001	.118	<.001	<.001
Pregnancies								
No. fetuses at birth, n (%)					<.001	<.001	<.001	<.001
1	4517 (71.4)	4591 (67.6)	31 062 (77.8)	948 695 (98.3)				
2	1614 (25.5)	1954 (28.8)	8548 (21.4)	16 489 (1.7)				
3 or 4	198 (3.1)	251 (3.7)	318 (0.8)	19 (<0.1)				
Deliveries								
Place of birth, n (%)					<.001	<.001	<.001	<.001
University hospital (level III)	4943 (78.1)	3993 (58.8)	17 154 (43.0)	299 470 (31.0)				
Central hospital (level II)	1340 (21.2)	2726 (40.1)	17 551 (44.0)	444 952 (46.1)				
Other[e]	41 (0.6)	77 (1.1)	5220 (13.1)	220 654 (22.9)				
Mode of delivery, n (%)					<.001	<.001	<.001	<.001
Vaginal	2524 (39.9)	3211 (47.2)	26 685 (66.8)	820 942 (85.1)				
Cesarean delivery	3793 (59.9)	3582 (52.7)	13 210 (33.1)	143 491 (14.9)				
Newborns								
Boys, n (%)	3428 (54.2)	3728 (54.9)	21 658 (54.2)	490 211 (50.8)	.426	.906	<.001	<.001
Birth wt, g, median (IQR)	1290 (1000–1570)	1970 (1730–2200)	2670 (2360–2985)	3590 (3276–3910)	<.001	<.001	<.001	<.001
≤1500 g (%)	4388 (69.3)	735 (10.8)	253 (0.6)	23 (<0.1)				
>1500 g (%)	1925 (30.4)	6053 (89.1)	39 654 (99.3)	964 935 (100)				
Wt by GA, n (%)					<.001	<.001	<.001	<.001
SGA	1019 (16.1)	883 (13.0)	3245 (8.1)	16 662 (1.7)				
AGA	4972 (78.6)	5637 (82.9)	34 681 (86.9)	919 970 (95.3)				
LGA	284 (4.5)	276 (4.1)	2002 (5.0)	28 571 (3.0)				
Apgar 1 min, median (IQR)	7 (5–8)	8 (7–9)	9 (8–9)	9 (9–9)	<.001	<.001	<.001	<.001
Apgar 1 min <4, n (%)	1001 (15.8)	325 (4.8)	890 (2.2)	7491 (0.8)	<.001	<.001	<.001	<.001
Admission to neonatal unit, n (%)	5692 (89.9)	5972 (87.9)	19 155 (48.0)	58 365 (6.0)	<.001	<.001	<.001	<.001
Ventilator, n (%)	3656 (57.8)	1413 (20.8)	1667 (4.2)	2793 (0.3)	<.001	<.001	<.001	<.001
Resuscitation at birth, n (%)	1901 (30.1)	625 (9.2)	795 (2.0)	3074 (0.3)	<.001	<.001	<.001	<.001
Phototherapy, n (%)	4202 (66.4)	3821 (56.2)	14 153 (35.4)	36 671 (3.8)	<.001	<.001	<.001	<.001
Antibiotic therapy, n (%)	4505 (71.2)	2958 (43.5)	5038 (12.6)	23 849 (2.5)	<.001	<.001	<.001	<.001
Death by 7 y of age, n (%)	13 (0.2)	4 (0.1)	36 (0.1)	627 (0.1)	.020	.009	<.001	.055
Age at death, y, median (IQR)	2.08 (1.42–4.52)	2.07 (1.04–3.25)	3.27 (2.04–4.92)	3.17 (1.92–4.94)	.477	.135	.099	.797

Years 1991–2008. Statistically significant differences were assessed by using Pearson's χ^2 test, Fisher's exact test, or the Mann–Whitney U test. Values of $P < .001$ were considered statistically significant. AGA, appropriate for gestational age; IQR, interquartile range.

[a] P = MP versus VP.

[b] P = LP versus VP.

[c] P = MP versus term.

[d] P = LP versus term.

[e] Regional hospital, private hospital, health center, or home birth.

TABLE 2 Sensory Disabilities in GA Groups

	VP <32 wk, *n* = 6329	MP 32 + 0/7–33 + 6/7 wk, *n* = 6796	LP 34 + 0/7–36 + 6/7 wk, *n* = 39 928	Term ≥37 wk, *n* = 965 203	Total, *n* = 1 018 256	*P*
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
Major sensory disabilities						
Hearing loss[a]	156 (2.46)	58 (0.85)	222 (0.56)	3365 (0.35)	3801 (0.37)	<.001
Years 1991–1995	46 (2.58)	23 (1.19)	72 (0.61)	1084 (0.37)	1225 (0.40)	
Years 1996–2001	79 (3.66)	22 (0.97)	100 (0.75)	1440 (0.46)	1641 (0.50)	
Years 2002–2008	31 (1.30)	13 (0.50)	50 (0.34)	841 (0.23)	935 (0.26)	
The age at diagnosis, y, median (IQR)	2.19 (0.49–4.76)	4.54 (2.22–5.92)	4.66 (1.67–5.94)	5.05 (2.82–6.03)	—	<.001
Visual disturbances or blindness[b]	230 (3.63)	133 (1.96)	475 (1.19)	7280 (0.75)	8118 (0.79)	<.001
Years 1991–1995	65 (3.65)	50 (2.58)	137 (1.16)	2213 (0.75)	2465 (0.80)	
Years 1996–2001	93 (4.31)	45 (1.98)	212 (1.59)	3070 (0.99)	3420 (1.04)	
Years 2002–2008	72 (3.01)	38 (1.47)	126 (0.85)	1997 (0.55)	2233 (0.61)	
The age at diagnosis y, median (IQR)	1.80 (0.49–4.34)	4.09 (2.50–5.01)	4.62 (3.35–5.59)	4.69 (3.51–5.57)	—	<.001
Minor sensory impairments						
Other ophthalmologic disorders[c]	819 (12.94)	434 (6.39)	1577 (3.95)	23 657 (2.45)	26 487 (2.60)	<.001
Years 1991–1995	202 (11.35)	129 (6.66)	435 (3.69)	6655 (2.27)	7421 (2.40)	
Years 1996–2001	340 (15.75)	166 (7.32)	631 (4.72)	9475 (3.06)	10 612 (3.24)	
Years 2002–2008	277 (11.59)	139 (5.37)	511 (3.46)	7527 (2.08)	8454 (2.21)	
ROP[d]	602 (9.51)	20 (0.29)	4 (0.01)	25 (0.00)	651 (0.06)	<.001
Years 1991–1995	23 (1.29)	0	1 (0.01)	5 (<0.01)	29 (0.01)	
Years 1996–2001	191 (8.85)	6 (0.26)	2 (0.01)	11 (<0.01)	210 (0.06)	
Years 2002–2008	388 (16.23)	14 (0.54)	1 (0.01)	9 (<0.01)	412 (0.11)	

Years 1991–2008 (*n* = 1 018 256). Infants who died before the age of 1 y (*n* = 2659), with congenital malformations (*n* = 13 007), or with missing data on GA (*n* = 5520) were excluded. Statistically significant differences were assessed by using Pearson's χ^2 test or independent samples Kruskal–Wallis test. Values of $P < .001$ were considered statistically significant. IQR, interquartile range.

[a] Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9): H90–91/389.

[b] Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9): H53–54/368–369.

[c] Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9): H49–52/367, 378.

[d] Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9): H35.1/362.22–27.

An estimated 19 million children have impaired vision, and 1.4 million children of the world are blind.[1] Hearing loss and blindness or low-level vision have been considered as some of the major impairments associated with preterm birth.[2] Childhood visual and hearing impairments constitute a major burden to children, families, and society. Children who are blind are at increased risks of socioeconomic problems, developmental delay, more frequent hospitalization, and death compared with children with sight.[3] Very preterm (VP) (<32 + 0/7 weeks) children in particular are more likely to have ophthalmic impairments compared with those born at term. Children born VP have 3 to 4 times poorer visual acuity and nearly 10 times more strabismus than term-born children.[4] The results of a few studies have also revealed increased ocular morbidity in infants born moderately preterm (MP) (32 + 0/7–33 + 6/7 weeks) and late preterm (LP) (34 + 0/7–36 + 6/7 weeks).[5,6]

The incidence of congenital hearing impairment has been estimated to be 1 to 2 per 1000 newborns, and, in risk populations, the incidence has been reported to be increased 10- to 50-fold.[7,8] VP birth, admission to a NICU, and low birth weight have been reported to increase the risk of hearing disabilities in childhood.[9–11]

Our aim with this study was to determine the incidences of sensory impairments in a large national birth cohort and to establish prenatal and neonatal risk factors predictive of these disabilities. To our knowledge, there are no large population-based reports that are focused on sensory impairments in MP and LP infants.

METHODS

All live births in Finland between 1991 and 2008 were collected from the medical birth register (MBR) (*n* = 1 039 263), as described with covariate definitions in detail in our earlier publications.[12–14] The MBR contains data on background factors of mothers, pregnancies, and live births with a birth weight ≥500 g or gestational age (GA) of at least 22 weeks, and the data have been validated and shown to be reliable.[15,16] Infants with missing data on GA (*n* = 5520; 0.53%), with at least 1 major congenital anomaly (*n* = 13 007; 1.25%), and those who died

TABLE 3 Risk Factor Analysis For Hearing Loss (n = 2576) Between 1996 and 2008 by Random Effect of the Number of Deliveries per Mother (n = 709 534)

	All Children (n = 2576/n = 709 534)			
	n	OR	(95% CI)	P
Mother				
Age, y				
<40	695 230	1.00	—	—
40 or more	14 304	1.03	(0.79–1.34)	.845
Smoking				
No	587 725	1.00	—	—
Yes	104 166	1.16[a]	(1.05–1.29)[a]	.005
Primipara				
No	413 927	1.00	—	—
Yes	295 607	0.80[a]	(0.69–0.92)[a]	.001
Previous cesarean delivery				
No	651 133	1.00	—	—
Yes	58 401	0.91	(0.79–1.06)	.249
Pregnancy				
No. fetuses				
1	688 342	1.00	—	—
2 or more	21 192	1.06	(0.81–1.39)	.659
Order of fetuses				
A	698 912	1.00	—	—
B or C	10 622	0.95	(0.66–1.37)	.778
Delivery				
Time of birth				
Monday to Friday 08:00–15:59	217 909	1.00	—	—
Monday to Friday 16:00–07:59	322 241	1.08	(0.98–1.18)	.127
Weekend	169 384	1.07	(0.96–1.20)	.203
Place of birth				
University hospital (level III)	235 046	1.00	—	—
Central hospital (level II)	325 935	1.09[a]	(1.00–1.20)[a]	.048
Other[b]	148 475	1.05	(0.94–1.18)	.377
Mode of delivery				
Vaginal	592 260	1.00	—	—
Cesarean delivery	116 874	1.10	(0.99–1.23)	.083
Newborn				
Sex				
Boy	362 073	1.00	—	—
Girl	347 461	0.95	(0.88–1.02)	.163
Gestational wt				
SGA	15 590	1.32[a]	(1.07–1.62)[a]	.009
LGA	20 546	1.14	(0.92–1.41)	.226
AGA	673 355	1.00	—	—
Apgar 1 min				
4–10	700 830	1.00	—	—
0–3	7501	1.55[a]	(1.22–1.97)[a]	<.001
Admission to neonatal unit				
No	641 777	1.00	—	—
Yes	67 753	1.32[a]	(1.13–1.53)[a]	<.001
Ventilator				
No	702 875	1.00	—	—
Yes	6659	2.11[a]	(1.59–2.79)[a]	<.001
Resuscitation at birth				
No	705 049	1.00	—	—
Yes	4485	1.12	(0.84–1.49)	.449
Antibiotic therapy				
No	680 482	1.00	—	—
Yes	29 052	1.29[a]	(1.04–1.58)[a]	.018
Sepsis (P36.0–8)[c]				
No	702 119	1.00	—	—
Yes	7415	0.83	(0.60–1.14)	.245
Intracranial hemorrhage (P52.0–9)[c]				

before the age of 1 year (n = 2659; 0.26%) were excluded. Data on major structural anomalies were derived from the register of congenital malformations and were excluded from the risk factor analysis as a significant confounding factor.[17] The remaining population (n = 1 108 265; 98.0% of all newborns) constituted the cohort for analysis. Children were analyzed in the following subgroups according to GA at birth: VP (<32 + 0/7 weeks; n = 6329), MP (32 + 0/7–33 + 6/7 weeks; n = 6796), LP (34 + 0/7–36 + 6/7 weeks; n = 39 928), and term (≥37 weeks; n = 965 203). The term group also included postterm infants (≥42 + 0/7 weeks; n = 47 318). GA was based on early pregnancy ultrasonography and was corrected according to whether there were marked discrepancies (5–7 days) between the initial estimation made by the last menstrual period. Three different time periods (1991–1995, 1996–2001, and 2002–2008) were compared. These periods were defined because Finland changed the classification system of diagnoses from the *International Classification of Diseases, Ninth Revision* (ICD-9) to the *International Classification of Diseases, 10th Revision* (ICD-10) in 1996, and the MBR changed the data collection forms in 1990 and 1996. The children were analyzed up to the age of 7 years or up to 2009.

Diagnoses of sensory disturbances were obtained from the hospital discharge register (HDR) and the register of the Social Insurance Institution (SII). The HDR contains data on inpatient and outpatient visits in all hospitals in Finland, and the data are considered to be reliable.[18] Diagnoses were coded according to the ICD-9 between 1991 and 1995 and according to the ICD-10 between 1996 and 2009. The SII register has data on granted medicine reimbursements and disability allowances. Data from the MBR, HDR, the register of congenital malformations, and the SII register

TABLE 3 Continued

	All Children (n = 2576/n = 709 534)			
	n	OR	(95% CI)	P
No	708 977	1.00	—	—
Yes	557	2.39[a]	(1.48–3.86)[a]	<.001
Convulsions (P90)[c]				
No	709 010	1.00	—	—
Yes	524	2.38[a]	(1.24–4.54)[a]	.009
Hyperbilirubinemia (P59.0–9)[c]				
No	675 247	1.00	—	—
Yes	34 287	0.89	(0.74–1.05)	.171
GA group				
Term (37 + 0/7–41 + 6/7 wk)	639 024	1.00	—	—
Postterm (≥42 + 0/7 wk)	32 951	1.07	(0.89–1.29)	.463
LP (34 + 0/7–36 + 6/7 wk)	28 151	1.26[a]	(1.04–1.52)[a]	.017[a]
MP (32 + 0/7–33 + 6/7 wk)	4859	1.14	(0.79–1.65)	.477
VP (<32 wk)	4549	2.34[a]	(1.75–3.14)[a]	<.001

A multivariate generalized linear mixed model was used, with results given as ORs with 95% CIs. Categories of missing values are not shown. AGA, appropriate for gestational age; —, not applicable.

[a] $P < .05$

[b] Regional hospital, private hospital, health center, or home birth.

[c] Associated ICD-10 codes.

were linked (between mothers and infants) via anonymized codes by the register-keeping authorities. Hearing loss (H90-H91/389) and visual disturbances or blindness (H53-54/368-369) were considered as major sensory disabilities, and the data were obtained from registers via *International Classification of Diseases* (ICD) codes that have also been used in other register studies.[19,20] Hearing loss included conductive and sensorineural hearing loss as well as other causes of hearing deficit according to ICD codes. Minor sensory defects were other ophthalmologic disorders including disorders of ocular muscles, binocular movement, refraction and accommodation (H49-H52/367, 378), and retinopathy of prematurity (ROP) (H35.1/362.22-27). In the Finnish health care system, these diagnoses are made in secondary or tertiary units by specialists. According to national recommendations, the otoacoustic emission was recommended to use for hearing screening of all newborns in Finland in 2004.

Infants born small for gestational age (SGA) were defined as those with a birth weight >2 SDs below the mean weight for GA (less than the fifth percentile), and infants born large for gestational age (LGA) were defined as those with a birth weight >2 SDs over the mean weight for GA (greater than the 95th percentile) according to Finnish sex-specific fetal growth curves.[21] The stratification of 1-minute Apgar scores to 0 to 3 and 4 to 10 was based on ICD-code definition of severe birth asphyxia as 1-minute Apgar scores 0 to 3.

The Mann–Whitney U test, the χ^2 test, independent samples Kruskal–Wallis test, or Fisher's exact test were used in group comparisons, as appropriate, and P values <.001 were considered statistically significant in group comparisons (Tables 1 and 2). A sensitivity analysis of incidences of impairments was done for those children who survived the first month of life to take into account the greater likelihood of survival with increasing GA. Risk factors of hearing loss and visual disturbances or blindness were sought by using a generalized linear mixed model with an lmer function as regards data recorded between 1996 and 2008 (Tables 3 and 4). A binary response (disability yes versus no) was used as a dependent variable, and the results of analysis were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All included explanatory variables shown in Tables 3 and 4 were modeled as fixed variables. The deliveries of any 1 mother constituted a potential source of variation; therefore, this subject-specific effect was included as a random effect in the models.[22] The generalized linear mixed model analyses were performed by using Statistical Package R, version 3.3.0 package lme4 (www.r-project.org), and the remaining analyses by using IBM SPSS Statistics version 23.0 software (IBM SPSS Statistics, IBM Corporation). Values of $P < .05$ (2-tailed) were considered statistically significant in mixed models.

RESULTS

Characteristics of the infants and mothers are shown in Table 1. The rate of VP birth was 0.62%, that of MP birth 0.67%, that of LP birth 3.92%, and the proportions of preterm births remained constant during the study. The MP and LP groups together constituted 88% of all preterm births and made up 28% of all admissions to neonatal units.

The incidences of sensory disabilities are presented in Table 2 and Fig 1. The incidence of hearing loss in the VP group was sevenfold greater, over twofold greater in the MP group, and, in the LP group, 1.5-fold greater than in the term group. Similarly, the incidences of visual disturbances or blindness and other ophthalmologic disorders decreased with advancing GA at birth. ROP was mostly presented in the VP group of infants. The incidences were mainly similar either after exclusion of infants who died before the age of 1 month or of infants who died before the age of 1 year (Supplemental Table 5).

Maternal smoking during pregnancy, being born SGA, an Apgar score <4 at 1 minute of age, admission to a neonatal unit, mechanical ventilation, intracranial hemorrhage, and

TABLE 4 Risk Factor Analysis For Visual Disturbances or Blindness ($n = 5653$) Between 1996 and 2008 by Random Effect of the Number of Deliveries per Mother ($n = 709\,534$)

	All Children ($n = 5653/n = 709\,534$)			
	n	OR	(95% CI)	*P*
Mother				
Age, y				
<40	695 230	1.00	—	—
40 or more	14 304	1.29[a]	(1.10–1.52)[a]	.002
Smoking				
No	587 725	1.00	—	—
Yes	104 166	1.48[a]	(1.38–1.58)[a]	<.001
Primipara				
No	413 927	1.00	—	—
Yes	295 607	0.96	(0.89–1.03)	.264
Previous cesarean delivery				
No	651 133	1.00	—	—
Yes	58 401	0.98	(0.88–1.08)	.663
Pregnancy				
No. fetuses				
1	688 342	1.00	—	—
2 or more	21 192	1.02	(0.84–1.23)	.845
Order of fetuses				
A	698 912	1.00	—	—
B or C	10 622	0.95	(0.74–1.22)	.694
Delivery				
Time of birth				
Monday to Friday 08:00–15:59	217 909	1.00	—	—
Monday to Friday 16:00–07:59	322 241	0.97	(0.91–1.04)	.378
Weekend	169 384	0.98	(0.91–1.05)	.509
Place of birth				
University hospital (level III)	235 046	1.00	—	—
Central hospital (level II)	325 935	0.62[a]	(0.58–0.66)[a]	<.001
Other[b]	148 475	0.59[a]	(0.54–0.63)[a]	<.001
Mode of delivery				
Vaginal	592 260	1.00	—	—
Cesarean delivery	116 874	0.98	(0.91–1.06)	.623
Newborn				
Sex				
Boy	362 073	1.00	—	—
Girl	347 461	0.97	(0.92–1.02)	.236
Gestational wt				
SGA	15 590	1.23[a]	(1.06–1.43)[a]	.006
LGA	20 546	1.12	(0.96–1.29)	.150
AGA	673 355	1.00	—	—
Apgar 1 min				
4–10	700 830	1.00	—	—
0–3	7501	1.27[a]	(1.05–1.54)[a]	.015
Admission to neonatal unit				
No	641 777	1.00	—	—
Yes	67 753	1.21[a]	(1.09–1.34)[a]	<.001
Ventilator				
No	702 875	1.00	—	—
Yes	6659	1.75[a]	(1.41–2.18)[a]	<.001
Resuscitation at birth				
No	705 049	1.00	—	—
Yes	4485	1.04	(0.83–1.32)	.717
Antibiotic therapy				
No	680 482	1.00	—	—
Yes	29 052	0.97	(0.83–1.12)	.647
Sepsis (P36.0–8)[c]				
No	702 119	1.00	—	—
Yes	7415	1.12	(0.90–1.39)	.320
Intracranial hemorrhage (P52.0–9)[c]				
No	708 977	1.00	—	—

convulsions during the neonatal period were associated with increased risks of both hearing loss and visual disturbances or blindness (Tables 3 and 4). Being born in other than level III hospitals and receiving antibiotic treatment during the first week of life predicted an increased risk of hearing loss. There was an association between primiparity and a decreased risk of hearing loss. Maternal age of ≥40 years was associated with an increased risk, and birth in other than a level III hospital was associated with a decreased risk of visual disturbances or blindness.

LP and VP births predicted an increased risk of hearing loss. LP, MP, and VP births were associated with an increased risk of visual disturbances or blindness after adjusting for background factors.

DISCUSSION

In this large national population-based cohort, the incidence of sensory impairments decreased with advancing GA at birth. Preterm birth was associated with an increased risk of visual disturbances or blindness, and VP and LP births predicted an increased risk of hearing loss. The most prominent risk factors associated with an increased risk of sensory impairment were intracranial hemorrhage and convulsions during the neonatal period.

Strengths and Limitations

The strength of this study is that it involves a population-based, complete national cohort with large numbers and reliable and validated health-register data. All children with neurodevelopmental disabilities are examined and diagnosed within the public health care system in Finland, which is easily accessible to all irrespective of socioeconomic status, employment, or family income. All children

TABLE 4 Continued

	All Children (n = 5653/n = 709 534)			
	n	OR	(95% CI)	P
Yes	557	2.13[a]	(1.43–3.16)[a]	<.001
Convulsions (P90)[c]				
No	709 010	1.00	—	—
Yes	524	2.88[a]	(1.78–4.64)[a]	<.001
Hyperbilirubinemia (P59.0–9)[c]				
No	675 247	1.00	—	—
Yes	34 287	0.92	(0.82–1.04)	.179
GA group				
Term (37 + 0/7–41 + 6/7 wk)	639 024	1.00	—	—
Postterm (≥42 + 0/7 wk)	32 951	0.92	(0.80–1.05)	.205
LP (34 + 0/7–36 + 6/7 wk)	28 151	1.31[a]	(1.16–1.49)[a]	<.001
MP (32 + 0/7–33 + 6/7 wk)	4859	1.42[a]	(1.11–1.80)[a]	.005
VP (<32 wk)	4549	1.94[a]	(1.55–2.44)[a]	<.001

A multivariate generalized linear mixed model was used, with results given as ORs with 95% CIs. Categories of missing values are not shown. AGA, appropriate for gestational age; —, not applicable.

[a] $P < .05$

[b] Regional hospital, private hospital, health center, or home birth.

[c] Associated ICD-10 codes.

under school age undergo routine regular physical and developmental assessments in child health centers, and, if any developmental problems are detected, children are referred to public special health care. Diagnoses in special health care are made according to multidisciplinary evaluations and clinical investigations, as appropriate according to national clinical guidelines. Diagnoses are immediately reported to register-keeping authorities by health care providers, this being obligatory according to Finnish legislation. We used linked data from several national health registers to obtain as complete a picture as possible, and this has been shown to be a reliable method.[23] Children with major congenital anomalies were excluded, because such anomalies represent a significant confounder when establishing risk factors of disabilities related to the perinatal period and prematurity.[24] Most of the children were analyzed up to early school age. Sensory impairments can reliably be diagnosed by that age.

The limitations of this study are consistent with those of all

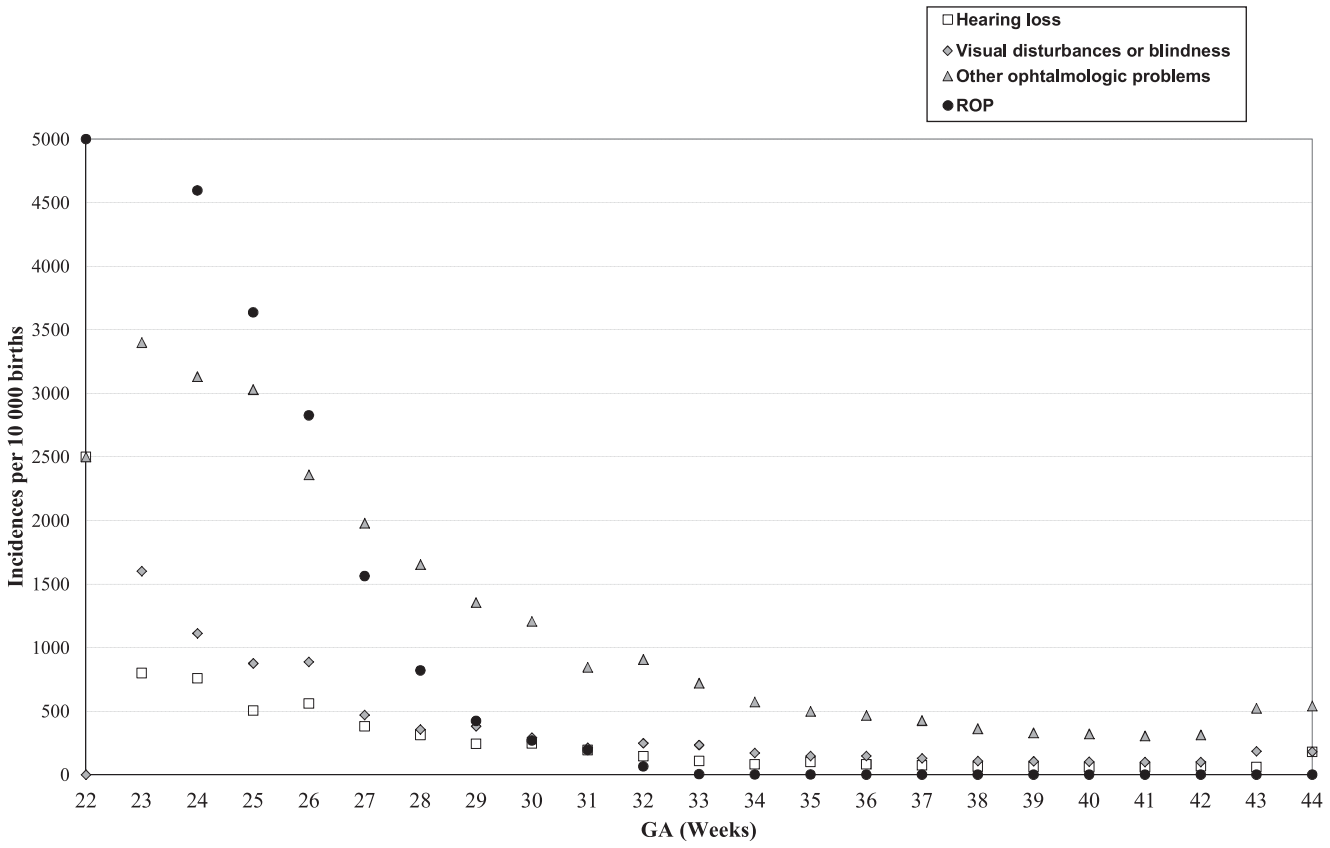

FIGURE 1
Incidences of sensory impairment per 10 000 births by GA at birth between 1991 and 2008 (n = 1 018 256).

observational register-based studies. Recording practices and clinical assessment tools may vary over time and between hospital districts, and this is considered to be the main limitation of our study. Because of the nature of this study, we had neither detailed information on the severity of disabilities nor on the functional situation of the children. On the other hand, it is obvious that established and recorded diagnoses constitute a burden to the children and their families. The follow-up period ended in 2009, so children born in the latest years of the study had a shorter follow-up time than the others. The follow-up time in the last time period (years 2002–2008) was probably too short for some of the children to allow making further conclusions of the trends of the incidences of impairments between 3 different time periods. A normal neonatal hearing screening result does not guarantee normal hearing later in childhood.[25] Thus, there might be some children in this population with as yet undiagnosed disabilities. Gaining access to the national health data is time consuming with a complex permission process. Thereafter, data collection and linkages were performed carefully and took time also. This led to a time gap from the follow-up time of the registers to the present time and can be also considered as a general limitation of register study.

Hearing Loss

The estimated rate of hearing loss has been reported to be 2 to 3 incidences per 1000 live births in the general population and 2 to 4 incidences per 100 infants in a higher risk population.[7,8,11] The overall incidence of hearing loss in our study was 0.37%, and it increased with decreasing GA at birth, being 2.46% in the VP group. These results are in accordance with those of earlier studies. In a nationwide cohort study of 2186 newborns in the Netherlands, the prevalence of hearing loss was 3.2% in infants born at <30 weeks of GA and/or birth weight <1000 g and treated in NICUs.[10] In a register-based study of 11 438 infants born before 33 weeks' gestation in Poland, hearing deficit was diagnosed in 4.2% of children born between weeks 26 and 28 and in 2.3% of children born between weeks 29 and 32.[11] In the current study, the incidences were also higher in MP and LP infants compared with term-born infants.

VP and LP births predicted an increased risk of hearing impairment in our study, whereas MP birth did not, compared with the term group. The apparent lack of impairments in the MP group is an unexpected finding, although incidences of hearing loss and visual disability were higher in the MP children compared with the LP and term children. It is unlikely that the MP group really contains risks that are not consistent with the VP and LP groups. The MP group was significantly smaller than the LP and term groups, which led to a decrease of statistical power. Some confounding factors may be used to explain the nonsignificant association of MP birth and hearing loss. In contrast to our findings, authors of a Norwegian case-control register study (327 cases and 391 992 controls) found that the risk of sensorineural hearing loss increased with decreasing birth weight, but length of gestation had no independent impact on the risk.[9] Also, in a French study of 1461 infants at risk for hearing impairment, birth before the 34th week of pregnancy did not show any influence on sensorineural hearing loss.[8] Contrasting results may be at least partly due to different outcome definitions between studies.

Intracranial hemorrhages and convulsions were the most prominent risk factors associated with hearing loss. These factors are obviously associated with brain injury, leading to worse outcome. Low Apgar scores at 1 minute, admission to a neonatal unit, mechanical ventilation, and antibiotic treatment predicted a risk of hearing loss. It has been suggested that loud noise in the neonatal unit environment and commonly used aminoglycosides cause toxic reactions in the inner ear of prematurely born infants, leading to hearing deficiencies.[26] Systemic hypoxia reduces cochlear oxygenation, causing adverse effects in cochlear function.[27] Low Apgar scores and mechanical ventilation can be considered as potential markers of hypoxia, and the association of these factors with hearing loss has also been found in other studies on preterm infants.[10,11] Intrauterine growth restriction has been considered to be one of the major mechanisms of sensorineural hearing loss.[9] In the current study, being born SGA and maternal smoking during pregnancy were predictors of hearing loss, and these factors may constitute a common pathway disturbing normal development of the fetal central nervous system and inner ear. Hyperbilirubinemia has been shown to be a risk factor of auditory nervous system damage and hearing loss.[28,29] Some studies have revealed this association, but interestingly, in our study this was not found.[11] This is probably due to the fact that we were not aware of bilirubin levels of the cases because of our study design. Thus, the cases with the highest bilirubin levels could not be identified.

Visual Impairment

Cerebral visual impairment is the most important cause of childhood severe visual impairment and blindness in developed countries.[3,30] Blindness has been reported as a long-term adverse outcome after extremely preterm birth (≤25 weeks of gestation), affecting 0.7% to 9% of such infants.[31] In our study,

preterm birth (<37 weeks) was associated with an increased risk of visual disturbances and blindness, compared with term birth. In a cross-sectional study of 182 children and adolescents (≤16 years of age) in New Zealand (143 blind and 39 children and adolescents with low vision), the main causes of blindness were asphyxia (25%), nonaccidental injury (7%), and prematurity (7%).[30] An association between smoking and an increased risk of visual disability was found in our study, as elsewhere.[32] The mother being >40 years of age predicted visual impairment, but antibiotic treatment had no such association. According to national guidelines, all high-risk pregnancies and preterm deliveries before 32 weeks' GA are centralized to level III hospitals in Finland. This may explain the association with a decreased risk of visual disturbances and blindness and birth in other than level III hospitals. Otherwise, risk factors were similar to those associated with hearing loss, intracranial hemorrhage, and convulsions being the most prominent risk factors of both disabilities.

The incidences of disorders of the ocular muscles, binocular movement, accommodation, and refraction decreased with increasing GA at birth. The incidence of these disabilities was 2.4 times higher in the MP group than in the term group. According to the results of a Swedish study of 78 children born between GAs of 32 and 36 weeks between 2002 and 2004, there was a significant difference in ocular motility deficits and refractive errors compared with term infants in the control group, and birth weight was found to be the strongest predictor of ophthalmologic abnormalities. In accordance with our results, they found that moderate-to-late preterm birth was associated with a 2.4-fold increased prevalence of refractive errors compared with children born full term.[6] Globally, ROP is considered to be a major threat to vision in preterm infants, and in our study, it was a problem of VP infants. It is possible that VP infants first diagnosed with ROP may later be diagnosed with blindness or other visual problems.

CONCLUSIONS

Preterm birth, including MP and LP births, increases the risk of adverse sensory outcomes. MP and LP groups constitute the majority of all prematurely born children, and impairments among these groups constitute a major burden to society and the health care system. The most prevalent risk factors associated with sensory disabilities were factors indicating brain damage arising in the perinatal period. The deleterious effects of smoking on the fetus should be mentioned in the counseling of pregnant women early in pregnancy. In addition, MP and LP infants with known risk factors of sensory impairment should have a low threshold for referral to further evaluation, to receive diagnosis and treatment as early as possible.

ABBREVIATIONS

CI: confidence interval
GA: gestational age
HDR: hospital discharge register
ICD: *International Classification of Diseases*
ICD-9: *International Classification of Diseases, Ninth Revision*
ICD-10: *International Classification of Diseases, 10th Revision*
LGA: large for gestational age
LP: late preterm
MBR: medical birth register
MP: moderately preterm
OR: odds ratio
ROP: retinopathy of prematurity
SGA: small for gestational age
SII: Social Insurance Institution
VP: very preterm

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REFERENCES

1. World Health Organization. Vision impairment and blindness. 2017. Available at: www.who.int/mediacentre/factsheets/fs282/en/. Accessed November 3, 2017
2. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med.* 2008;359(3):262–273
3. Solebo AL, Teoh L, Rahi J. Epidemiology of blindness in children. *Arch Dis Child.* 2017;102(9):853–857
4. Cooke RW, Foulder-Hughes L, Newsham D, Clarke D. Ophthalmic impairment at 7 years of age in children born very preterm. *Arch Dis Child Fetal Neonatal Ed.* 2004;89(3):F249–F253
5. Robaei D, Kifley A, Gole GA, Mitchell P. The impact of modest prematurity on visual function at age 6 years: findings from a population-based

study. *Arch Ophthalmol*. 2006;124(6):871–877

6. Raffa L, Aring E, Dahlgren J, Karlsson AK, Andersson Grönlund M. Ophthalmological findings in relation to auxological data in moderate-to-late preterm preschool children. *Acta Ophthalmol*. 2015;93(7):635–641
7. Meyer C, Witte J, Hildmann A, et al. Neonatal screening for hearing disorders in infants at risk: incidence, risk factors, and follow-up. *Pediatrics*. 1999;104(4 pt 1):900–904
8. Ohl C, Dornier L, Czajka C, Chobaut JC, Tavernier L. Newborn hearing screening on infants at risk. *Int J Pediatr Otorhinolaryngol*. 2009;73(12):1691–1695
9. Engdahl B, Eskild A. Birthweight and the risk of childhood sensorineural hearing loss. *Paediatr Perinat Epidemiol*. 2007;21(6):495–500
10. Hille ET, van Straaten HI, Verkerk PH; Dutch NICU Neonatal Hearing Screening Working Group. Prevalence and independent risk factors for hearing loss in NICU infants. *Acta Paediatr*. 2007;96(8):1155–1158
11. Wroblewska-Seniuk K, Greczka G, Dabrowski P, Szyfter-Harris J, Mazela J. Hearing impairment in premature newborns-analysis based on the national hearing screening database in Poland. *PLoS One*. 2017;12(9):e0184359
12. Hirvonen M, Ojala R, Korhonen P, et al. Cerebral palsy among children born moderately and late preterm. *Pediatrics*. 2014;134(6). Available at: www.pediatrics.org/cgi/content/full/134/6/e1584
13. Haataja P, Korhonen P, Ojala R, et al. Asthma and atopic dermatitis in children born moderately and late preterm. *Eur J Pediatr*. 2016;175(6):799–808
14. Hirvonen M, Ojala R, Korhonen P, et al. Intellectual disability in children aged less than seven years born moderately and late preterm compared with very preterm and term-born children - a nationwide birth cohort study. *J Intellect Disabil Res*. 2017;61(11):1034–1054
15. Gissler M, Teperi J, Hemminki E, Meriläinen J. Data quality after restructuring a national medical registry. *Scand J Soc Med*. 1995;23(1):75–80
16. Gissler M, Shelley J. Quality of data on subsequent events in a routine Medical Birth Register. *Med Inform Internet Med*. 2002;27(1):33–38
17. European Surveillance of Congenital Anomalies. EUROCAT guide 1.3 and reference documents. Instructions for the registration and surveillance of congenital anomalies. Available at: http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistratio/guide13instructionmanual. Accessed April 15, 2018
18. Sund R. Quality of the Finnish hospital discharge register: a systematic review. *Scand J Public Health*. 2012;40(6):505–515
19. Korvenranta E, Lehtonen L, Peltola M, et al. Morbidities and hospital resource use during the first 3 years of life among very preterm infants. *Pediatrics*. 2009;124(1):128–134
20. Korvenranta E, Linna M, Rautava L, et al; Performance, Effectiveness, and Cost of Treatment Episodes (PERFECT) Preterm Infant Study Group. Hospital costs and quality of life during 4 years after very preterm birth. *Arch Pediatr Adolesc Med*. 2010;164(7):657–663
21. Pihkala J, Hakala T, Voutilainen P, Raivio K. [Characteristic of recent fetal growth curves in Finland]. *Duodecim*. 1989;105(18):1540–1546
22. Fitzmaurice G, Laird N, Ware J. *Applied Longitudinal Analysis*, 2nd ed. Hoboken, NJ: John Wiley and Sons; 2011
23. Gissler M, Hemminki E, Louhiala P, Järvelin MR. Health registers as a feasible means of measuring health status in childhood–a 7-year follow-up of the 1987 Finnish birth cohort. *Paediatr Perinat Epidemiol*. 1998;12(4):437–455
24. Walden RV, Taylor SC, Hansen NI, et al; National Institute of Child Health and Human Development Neonatal Research Network. Major congenital anomalies place extremely low birth weight infants at higher risk for poor growth and developmental outcomes. *Pediatrics*. 2007;120(6). Available at: www.pediatrics.org/cgi/content/full/120/6/e1512
25. van Noort-van der Spek IL, Goedegebure A, Hartwig NG, Kornelisse RF, Franken MJP, Weisglas-Kuperus N. Normal neonatal hearing screening did not preclude sensorineural hearing loss in two-year-old very preterm infants. *Acta Paediatr*. 2017;106(10):1569–1575
26. Zimmerman E, Lahav A. Ototoxicity in preterm infants: effects of genetics, aminoglycosides, and loud environmental noise. *J Perinatol*. 2013;33(1):3–8
27. Haupt H, Scheibe F, Ludwig C. Changes in cochlear oxygenation, microcirculation and auditory function during prolonged general hypoxia. *Eur Arch Otorhinolaryngol*. 1993;250(7):396–400
28. De Vries LS, Lary S, Whitelaw AG, Dubowitz LM. Relationship of serum bilirubin levels and hearing impairment in newborn infants. *Early Hum Dev*. 1987;15(5):269–277
29. Shapiro SM, Nakamura H. Bilirubin and the auditory system. *J Perinatol*. 2001;21(suppl 1):S52–S55; discussion S59–S62
30. Chong C, Dai S. Cross-sectional study on childhood cerebral visual impairment in New Zealand. *J AAPOS*. 2014;18(1):71–74
31. Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. *Pediatr Neurol*. 2015;52(2):143–152
32. Adhikari S, Shrestha MK, Adhikari K, Maharjan N, Shrestha UD. Factors associated with childhood ocular morbidity and blindness in three ecological regions of Nepal: Nepal pediatric ocular disease study. *BMC Ophthalmol*. 2014;14:125

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