PRETERM DELIVERY AND ITS ASSOCIATION WITH FALSE POSITIVE, AUDITORY BRAINSTEM RESPONSE (ABR)-BASED NEWBORN HEARING SCREENING FINDINGS

By

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ABSTRACT

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Newborn hearing screening failure can occur in infants without hearing loss; these false-positive (FP) results have been speculated to reflect neurodevelopmental disorder risk. Preterm birth (PTB), a known neurodevelopmental risk factor, has been associated with FP at initial screening. We aim to further characterize this association by stratifying PTB by gestational age and delivery circumstance. To do this, we analyzed birth certificate and Early Hearing Detection & Intervention data from the Michigan Dept. of Health & Human Services (2007–2015; n = 919,363). We restricted our analysis to singleton live births with available ABR-based hearing screening data and obstetric estimates of gestational age (n = 655,079). We then used logistic regression to evaluate the association of PTB defined by gestational age (extreme: < 28 weeks; moderate: 28–34 weeks; late: 34–36 weeks) and delivery circumstance (spontaneous, medically indicated) with FP, using full-term birth (≥ 37 weeks) as the referent group. Approximately 4% of infants had FP findings. All gestational age categories were associated with this phenomenon (extreme: OR = 4.2, 95% CI 3.7, 4.7; moderate: OR = 1.2, 95% CI 1.1, 1.3; late: 1.6, 95% CI 1.5, 1.7). Spontaneous and medically indicated PTB were also associated with FP (OR = 1.7, 95% CI 1.6, 1.8; OR = 1.4, 95% CI 1.3, 1.5, respectively). All results persisted following adjustment for socio-demographic and antepartum factors except for moderate PTB (OR = 1.0, 95% CI 0.9, 1.1), though sensitivity analyses suggested marked heterogeneity within this group. Further research is needed to investigate factors underlying these differences and whether they correlate with neurodevelopmental disorder diagnoses.

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KEY TO ABBREVIATIONS

PT	Preterm
PTB	Preterm birth
ABR	Auditory brainstem response
FP	False positive
ASD	Autism spectrum disorder
ADHD	Attention deficit/hyperactivity disorder
CP	Cerebral palsy
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
EHDI	Early Hearing Detection & Intervention
PROM	Premature rupture of membranes
OR	Odds ratio
CI	Confidence interval
F/U	Follow-up
MI	Medically indicated

1. INTRODUCTION

1.1 Preterm Delivery: Prevalence and associated morbidities

Preterm birth (PTB), defined as any birth occurring before 37 completed weeks of gestation, accounts for approximately 10% of live births in the United States [1]. During the prenatal period, the organ systems of a developing infant undergo important developmental and maturational processes. During the first trimester, the groundwork is laid for all body structures and organ systems, which increase rapidly in size [2]. The fetus continues to grow throughout the second trimester, at the end of which many organs are well developed. This maturation process continues into the third and final trimester, which is when PTB typically coincides and when a fetus born early may be viable outside the womb [2]. During this timeframe, infants gain most of their birth weight; the alveoli of the lungs begin to develop, allowing for respiration; and the brain grows rapidly in size due to synaptogenesis and myelination [2-4]. Although preterm infants continue to develop during the postnatal period, the early transition to the extrauterine environment may affect developmental processes and the viability of the infant [5 6]. Indeed, although many preterm infants develop typically, PTB is known to be a leading cause of infant mortality and morbidity, with preterm infants having a greater risk for complications such as respiratory distress, sepsis, necrotizing enterocolitis, and intraventricular hemorrhage [1 7-9]. Preterm infants are also at an increased risk for a range of longer-term negative health outcomes throughout the lifespan, such as increased mortality; metabolic problems; and sensory, cardiovascular, pulmonary, and neurodevelopmental disorders, the latter of which include both milder, subclinical difficulties and those that meet full diagnostic criteria [1 8-16].

The heterogeneity in health outcomes linked to preterm birth reflects not only how early disruptions in development may have many different downstream effects, but also the great

heterogeneity in preterm birth itself. For example, gestational week at delivery varies widely within the preterm range and risk for negative health sequelae increases as gestational age decreases within this range [9-13 17]. Although the cutpoints that define gestational age range subgroups vary slightly from one study to the next, commonly employed definitions include: late preterm (34–36 weeks), moderately preterm (28–34 weeks) and extremely preterm (< 28 weeks), [18-20]. In the United States, approximately 75% of preterm births fall into the late preterm category, whereas approximately 20% are moderate and 5% are extreme [18-21].

In addition to variability in gestational age at delivery, preterm births also vary according to delivery circumstance. Some are spontaneous, which is when labor or rupture of membranes spontaneously occurs, while others are medically indicated, which is when the medical provider determines that continuing the pregnancy would place either the mother and/or infant at risk of negative outcomes [1 10 22]. Medically indicated preterm births have been disproportionately associated with hypertensive and metabolic disorders during pregnancy, while spontaneous preterm births may be more associated with inflammatory processes [23-29]. The different pathological mechanisms behind different delivery circumstances may have different effects on fetal development and subsequent risk of health outcomes. Approximately 20–30% of preterm births are medically indicated, while the remainder are spontaneous [22 30].

1.2 Preterm Delivery and Neurodevelopmental Disorders

Neurodevelopmental disorders reflect alterations in brain development and functioning compared to typically developing peers and typically manifest in infancy or childhood [31 32]. Some examples of neurodevelopmental disorders include autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), intellectual disability, communication disorders, specific learning disorders, and motor disorders such as cerebral palsy (CP) [31 32]. These

disorders tend to persist throughout the lifespan and can create difficulties across various contexts, such as in an individual's academic, social, or professional life, which has implications on mental and physical health, access to care, educational and professional achievement, occupational functioning, interpersonal relationships, life expectancy, quality of life, and financial stability [31 33-50]. However, timely enrollment in early intervention services helps improve outcomes for children with neurodevelopmental disorders [51-59]. As a result, it is important to identify individuals at risk for neurodevelopmental disorders as early as possible. However, at times, these diagnoses are not made until toddlerhood or beyond, as disturbances may be subtle and are typically based on behavioral observations [56 57 59 60].

Contributing to this difficulty is that neurodevelopmental disorders are highly heterogeneous, even within the same diagnostic category. Perhaps not surprisingly, multiple risk factors, both endogenous and exogenous, have been identified [31 60 61]. A common conceptualization of neurodevelopmental disorders posits that small, basic-level alterations in brain development may have cascading effects as the brain develops and interacts with genetic and environmental factors, producing atypical developmental trajectories with diverse outcomes [60]. In the case of neurodevelopmental disorders among those born preterm, it is commonly hypothesized that there may be an insult to brain development during the pre- or perinatal period [11]. This may include factors that are experienced during the in-utero (maternal complications), antepartum (delivery complications), or ex-utero environment (e.g., postnatal complications; medical interventions).

An outstanding question is whether heterogeneity in preterm birth can explain, in part, the heterogeneity in neurodevelopmental outcomes linked to early delivery. Studies assessing the effect of gestational age at delivery have shown that, while all preterm subgroups exhibit higher

risk for neurodevelopmental disorders compared to full-term counterparts, this risk increases with decreasing gestational age [9 11-13 17 62]. This pattern of findings has been observed robustly across a voluminous literature. In contrast, only a handful of studies have examined whether delivery circumstance is associated with neurodevelopmental disorder risk. To date, findings are mixed, with some studies reporting a greater risk in spontaneous preterm birth, others reporting a greater risk in medically indicated preterm birth, and others reporting no difference between the two types of deliveries. [23 63-65].

1.3 Perinatal brain assessment and neurodevelopmental disorders

It may be possible to use biomarkers to detect atypical development associated with the hypothesized developmental insults implicated in neurodevelopmental disorders. For example, measures of brain structure or function that are assessed during the perinatal period, closer to the time of the proposed insult, would be particularly informative. If biomarkers can inform risk before behavioral symptoms emerge, this represents an opportunity to improve developmental surveillance for at-risk infants and perhaps elucidate etiologic pathways involved.

Of the few measures available that can assess perinatal brain development, the most common clinical modalities include ultrasound and magnetic resonance imaging (MRI) [62 66-71]. Studies using these measures have identified various patterns in brain lesions that appear to predict increased risk of neurodevelopmental disorders, such as CP, particularly among preterm infants [66-71]. However, these studies suffer from various limitations. For example, extensive resources are required to collect ultrasound or MRI data, and thus, these studies tend to have relatively small samples [67 69-71]. In addition, there is usually a medical indication to receive these assessments, as most studies are performed with NICU-admitted preterm infants and lack healthy controls, leading to confounding by indication [66 67 69-71].

1.4 An alternative perinatal, brain-based measure: Auditory brainstem responses (ABRs)

An alternative brain-based measure that addresses these limitations is the auditory brainstem response (ABR), which is a common target for universal newborn hearing screening in Michigan. ABRs are an electrophysiological measure of neural activity from the auditory nerve through the brainstem in response to broadband auditory stimulation [72]. This response is depicted graphically as a wave (Figure 1), with the peaks in activity corresponding to the electrical signal reaching different key structures along the pathway from the auditory nerve through the brainstem [72]. Because newborn infants are screened at hospital discharge, ABR-based data from the perinatal period are available at the population level and irrespective of perinatal risk. ABRs are non-invasively recorded using electrodes placed on the scalp while infants are sleeping, making them easier to administer to infants without medical indications.

ABRs can be assessed at either the screening level or diagnostic level. At the screening level, the morphology of the ABR is assessed automatically by computer software, which evaluates whether the infant passed or failed the test based on the overall presence of abnormalities in the waveform [73 74]. Infants who do not have detectable abnormalities in the hearing screen receive a “pass” result, meaning the brain has produced the expected response to stimulation by sound, whereas those with abnormalities in their response receive a “fail” result and are referred to further testing at the diagnostic level [73]. At the diagnostic level, a high resolution assessment is conducted to assess hearing loss through a more precise characterization of the ABR’s latencies and amplitudes [73].Therefore, although diagnostic-level information is available on a subset of infants who failed their newborn hearing screen, screening-level data are available at the population level, as nearly all infants born in Michigan have their hearing screened using ABRs at hospital discharge.

Approximately 96% of infants pass this state-mandated screening, but 4% fail and are referred for diagnostic hearing assessment [73 75]. However, of the infants who failed the initial screening and received diagnostic follow-up, nearly 94% do not have evidence of hearing loss (i.e., false positives). [73 75]. This means that many of the infants who have abnormalities in their ABRs at the screening level during the perinatal period do not have hearing loss.

1.5 ABRs and neurodevelopmental disorders

Researchers have investigated whether these false positives in newborn hearing screening reflect an abnormality in perinatal brain development. This is because ABR alterations have been cross-sectionally associated with neurodevelopmental disorders [76-78], and recently, a few studies suggest that ABR alterations in the perinatal period may be associated with later diagnosis of neurodevelopmental disorders [79-82]. However, most studies use in-depth, diagnostic-level characterizations of the ABR waveform rather than the lower resolution assessments used in newborn hearing screening, so it is unclear whether similar associations would be observed between false positives in newborn hearing screening and neurodevelopmental disorders at the population level.

1.6 ABRs and preterm delivery

Based on this knowledge and the fact that preterm delivery is an established risk factor for neurodevelopmental disorders, we are interested in exploring whether preterm birth is associated with alterations in screening-level ABR findings at birth and whether any patterns observed relate to heterogeneity in preterm birth. Previous studies comparing preterm infants to full-term infants using high-resolution ABR assessments have demonstrated that preterm infants have alterations in the characteristics of their ABRs compared to full-term infants, even when assessed at term age, but little research has been done specifically looking at similar associations

between preterm birth and false positives in ABR-based newborn hearing screening [83]. This is a significant gap in the literature considering that, if false-positive ABR screens are associated with an increase in risk of neurodevelopmental disorders, ABR screening may be useful in identifying infants at increased risk of neurodevelopmental disorders. This would allow us to use existing infrastructure to potentially identify at-risk infants at a much earlier age than when the behavioral signs of neurodevelopmental disorders begin to appear. This, in turn, would allow for more tailored surveillance efforts and perhaps even earlier intervention service enrollment.

An additional gap in this literature is that most studies of ABRs and preterm birth do not acknowledge the great heterogeneity in preterm birth. For example, gestational age differs among preterm infants, and lower gestational ages are associated with greater risk for negative health sequelae, as described above. However, studies on ABRs and preterm birth have defined gestational age subgroups inconsistently across studies, making findings difficult to compare. That said, a recent meta-analysis has shown that lower gestational age increases risk of ABR alterations independent of NICU admission [83]. Second, delivery circumstances differ across preterm births, but the distinction between spontaneous and medically indicated deliveries has not been made in the literature on ABRs and preterm birth. This is an important gap considering that the etiological mechanisms behind different delivery circumstances may have differing effects on brainstem maturation and fetal development in general.

1.7 The current study

This thesis has two aims. First, we will assess the association between preterm delivery and false positives in ABR-based newborn hearing screening in Michigan. Preterm infants will be compared to full-term infants, and we hypothesize that preterm infants will be more likely to have false-positive ABR screens. Second, we aim to further characterize the association between

different preterm delivery subtypes and false-positive ABR screens to assess whether there are any differences in risk according to gestational age or delivery circumstance.

For gestational age, preterm infants will be categorized as 1) late preterm (34–36 weeks of gestation), 2) moderately preterm (28–34 weeks of gestation), and 3) extremely preterm (< 28 28 weeks). All gestational age subcategories will be compared to full-term births, and we hypothesize that the lower the gestational age, the more likely an infant will be to have false-positive ABR screening results, given that lower gestational age is robustly associated with a greater risk of neurodevelopmental disorders [8-10].

For delivery circumstance, both medically indicated and spontaneous preterm births will be compared to full-term births. We hypothesize that medically indicated and spontaneous preterm birth will be associated with false-positive newborn hearing screening results relative to full-term births. However, it is unclear whether the magnitude of associations will differ between medically indicated and spontaneous preterm births, as there are few studies on delivery circumstance and ABR characteristics or risk of neurodevelopmental disorders.

2. METHODS

2.1 Study Population & Design

We performed a secondary analysis of administrative health records maintained by the Michigan Dept. of Health and Human Services. Data sources included Michigan birth certificates using the 2003 revision of the US Standard Certificate of Live Birth (2007–2015) and linked data from the Early Hearing Detection & Intervention (EHDI) program (n = 919,363). Eligibility criteria included singleton births, availability of an obstetric estimate of gestational age, receipt of ABR-based hearing screening, and no known diagnosis of hearing loss, yielding an analytic sample of 651,391 births (Figure 2). The study was deemed exempt by the institutional review boards of both Michigan State University and the Michigan Department of Health and Human Services.

2.2 Measures

2.2.1 Preterm birth

Preterm birth and its gestational age-based subcategories were defined using the best obstetric estimate of gestational age from the birth certificate (preterm: < 37 weeks; extreme: < 28 weeks; moderate: 28–34 weeks; late: 34–36 weeks). Delivery circumstance was defined using a validated algorithm that classifies preterm birth as spontaneous if the birth certificate indicated: 1) premature rupture of membranes (PROM), 2) evidence of labor (e.g., prolonged, precipitous, augmentation, or trial of labor) in the absence of induction, or 3) vaginal delivery in the absence of PROM, labor, or induction. Births where the birth certificate noted induction or cesarean section (in the absence of PROM, labor, or induction) were classified as medically indicated [84].

2.2.2 ABR-based hearing screening results

False-positive, ABR-based hearing screening results included infants who failed their initial, state-reported screen (either ear) despite having no diagnosis of hearing loss in EHDI records. True-negative, ABR-based results included infants who passed their initial, state-reported screen (both ears) and did not have any diagnosis of hearing loss in EHDI records.

2.2.3 Covariates

Maternal sociodemographics, including race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Native American, Asian/Pacific Islander, other), highest level of education (less than high school, high school or equivalent, some college, college degree, professional school), age at delivery (< 18, 18–25, 25–35, ≥ 35), insurance status (private, Medicaid, self-pay, other), and smoking status (smoker, non-smoker) were obtained from birth certificate data. Infant characteristics obtained from birth certificates included sex, NICU admission (any, none), 5-minute Apgar score (< 3, 4–6, 7–10), and presence of congenital anomalies (any, none). Corrected age at initial screening was calculated as the sum of gestational age at delivery and the time between birth and initial screening (< 37 weeks: preterm age at screening; ≥ 37 weeks: term-equivalent age at screening).

2.3 Analysis Plan

We began by comparing the distribution of all study variables across the original, linked dataset and the analytic sample to characterize impacts of our inclusion/exclusion criteria. Next, we evaluated the distribution of all covariates across gestational age subgroups and delivery circumstance. Our main analysis used a logistic regression model to evaluate the association between preterm delivery and false-positive ABR-based hearing screening results using full-term delivery as the referent group. The analysis was then repeated with preterm birth divided into

gestational age-based subgroups, delivery circumstance-based subgroups, and gestational age-based subgroups stratified by delivery circumstance. We then repeated these analyses following adjustment for the sociodemographic and infant characteristics described above. Finally, we performed sensitivity analyses evaluating whether findings differed by corrected age at screening and whether findings persisted following exclusion of infants with congenital anomalies and infants lost to follow-up. All tests were two-tailed with an alpha of 0.05.

3. RESULTS

3.1 Sample Description

Following the application of our inclusion/exclusion criteria, we found that our sample was generally representative of the live births in Michigan during the study timeframe (2007–2015) (Table 1). The exception was race/ethnicity, where we observed a slight underrepresentation of non-Hispanic Black (15% vs. 18%) and overrepresentation of non-Hispanic White birthing people (72% vs. 69%) in the analytic sample.

We then examined how maternal sociodemographics and perinatal characteristics were associated with preterm birth according to gestational age (Table 2a) and delivery circumstance (Table 2b). We observed that compared to birthing people who delivered at term, non-Hispanic Black race/ethnicity, Medicaid enrollment, and lower levels of education were represented in greater proportions among the lower gestational age groups. Older corrected age at hearing screening, loss to follow-up, NICU admission, and congenital anomalies were also overrepresented in the lower gestational age groups. For delivery circumstance, non-Hispanic Black race/ethnicity as well as congenital anomalies, NICU admission, and Apgar scores below 7 were disproportionately represented among spontaneous and medically indicated preterm births relative to full-term births. However, spontaneous preterm birth included greater proportions of birthing people who smoked, had lower levels of education, were non-Hispanic Black, or were younger or enrolled in Medicaid compared to medically indicated birth. Infants who were male or were lost to follow-up also were represented in greater proportions among spontaneous compared to medically indicated preterm births. However, NICU admission was more common among the medically indicated subgroup.

3.2 Unadjusted Analysis

Approximately 4% of infants had false-positive, ABR-based hearing screening findings, and we observed that preterm birth (< 37 weeks) was associated with this phenomenon (Table 3; OR = 1.6, 95% CI 1.5, 1.7), irrespective of whether it was defined by gestational age subgroups (extreme: OR = 4.2, 95% CI 3.7, 4.7; moderate: OR = 1.2, 95% CI 1.1, 1.3; late: OR = 1.6, 95% CI 1.5, 1.7) or delivery circumstance (spontaneous: OR = 1.7, 95% CI 1.6, 1.8; medically indicated: OR = 1.4, 95% CI 1.3, 1.5). Within gestational age subgroups, the extreme preterm estimate was stronger than the moderate and late preterm estimates, and the late preterm estimate was stronger than the moderate preterm estimate. Estimates did not differ between the spontaneous and medically indicated preterm groups (e.g., extreme spontaneous: OR = 4.5, 95% CI 3.8, 5.2; extreme indicated: OR = 3.8, 95% CI 3.1, 4.7). Following the stratification of gestational age by delivery circumstance, we observed that all preterm subgroups were again associated with false-positive findings relative to full-term birth. Gestational age-based findings did not differ according to delivery circumstance except for late preterm birth, where spontaneous delivery was more strongly associated with false positive findings than medically indicated delivery (OR = 1.7, 95% CI 1.3, 1.5, and OR = 1.4, 95% CI 1.3, 1.5, respectively).

3.3 Adjusted Analysis

All of the above associations were attenuated following adjustment for covariates, with the gestational age-based estimates decreasing by 13 to 21% and delivery circumstance-based estimates decreasing by 7 to 12% (Table 3). However, all findings exceeded significance thresholds except for the moderate preterm group (OR = 1.0, 95% CI 0.9, 1.1). This attenuation was observed among both the spontaneous and medically indicated moderate preterm births (OR = 1.0, 95% CI 0.9, 1.2, and OR = 1.0, 95% CI 0.9, 1.2, respectively).

3.4 Sensitivity Analyses

To examine whether corrected age at screening modified any of the previous findings, we repeated our analyses after stratifying gestational age and delivery circumstance by this variable (Table 4). Although preterm infants screened at term-equivalent or preterm age had greater odds of obtaining false-positive results compared to full-term infants, the association was stronger among preterm infants screened at term-equivalent age (OR = 3.3, 95% CI 2.6, 4.1) compared to preterm age (OR = 1.6, 95% CI 1.5, 1.7). We also observed this pattern among moderate preterm births (OR = 3.9, 95% CI 2.5, 6.2; OR = 1.2, 95% CI 1.1, 1.3) as well as spontaneous (OR = 3.1, 95% CI 2.2, 4.2; OR = 1.7, 95% CI 1.6, 1.8) and medically indicated preterm births (OR = 3.5, 95% CI 2.6, 4.8; OR = 1.4, 95% CI 1.3, 1.5). When gestational age subgroups were stratified by delivery circumstance, estimates did not differ according to corrected age except among moderate preterm births. Again, screening at term-equivalent age was more strongly associated with false-positive findings than screening at preterm age. In addition, medically indicated moderate preterm birth was more strongly associated with false-positive findings than spontaneous moderate preterm birth, irrespective of the corrected age at screening.

All of the above findings were unaffected following the exclusion of infants with congenital anomalies and infants lost to follow-up (Tables 5–6).

4. DISCUSSION

4.1 Overall findings: Summary

We assessed the association between preterm birth and false-positive, ABR-based newborn hearing screening findings using Michigan birth certificates and linked EHDI data. We found a moderate, positive association between preterm birth and false-positive results. We then further characterized this association by gestational age and delivery circumstance. Our analysis of gestational age revealed that all three preterm gestational age-based subgroups had elevated odds of false-positive results compared to full-term infants. The strongest association was observed in the extreme PTB subgroup, followed by late PTB, and then moderate PTB. The associations for extreme and late PTB remained significant following adjustment for covariates, but the small association observed with moderate PTB no longer differed from that of full-term infants. The analysis of delivery circumstance found an increased odds of false positives for both subgroups compared to full-term infants, but suggested a slightly greater, though non-significant, association among spontaneous PTB compared to medically indicated PTB. When gestational age subgroups were stratified by delivery circumstance, similar patterns were observed to the unstratified analyses, with a slightly stronger association for spontaneous PTB within each age group and the strongest associations observed among the extreme PTB subgroups. Findings were unchanged following the exclusion of children who were lost to follow-up in the EHDI program as well as children with evidence of congenital anomalies from birth certificate data.

4.2 Discussion of findings

4.2.1 Gestational age

Our findings regarding gestational age are generally consistent with previous research linking decreasing gestational age with increasing risk for infant mortality, newborn morbidities,

and neurodevelopmental disorders. For example, much like this previous literature, we observed our strongest associations with extreme PTB and found that odds of false-positive findings were greater among late PTB than among full-term infants. However, our results also suggest that associations between gestational age and false-positive findings were not fully linear, given that following adjustment, odds among moderate PTB were indistinguishable from infants born full-term. This may be because moderate PTB reflects a particularly heterogeneous group of infants. Indeed, when we stratified this group by corrected age at screening (a proxy for severity of newborn morbidity and maturation), we observed that moderate preterm infants screened at term-equivalent age had odds of false-positive findings that were similar to extreme PTB. However, this association was much smaller and became non-significant following adjustment among moderate preterm infants screened at preterm age.

4.2.2 Delivery circumstance

The literature on delivery circumstance and neurodevelopmental disorders is inconsistent, with some studies finding a greater risk among spontaneous PTB [23] and others among medically indicated PTB [64 65], while others have found no significant differences [63]. Our analysis of delivery circumstance suggested a slightly stronger association with false-positive results in spontaneous PTB compared to medically indicated PTB, although the confidence intervals for these two subgroups overlap. Our findings suggest there may be a slight difference between the two subtypes that may relate to different etiological mechanisms. When stratified by corrected age at screening, we found that infants assessed at a term-equivalent age had much stronger associations with false-positive findings than those screened at preterm age within both delivery circumstance subgroups. This may suggest that neonatal morbidity, which is associated with longer hospital stays, and other postnatal factors such as NICU treatment, may play an

important role in false-positive findings irrespective of delivery circumstance (see 4.2.4 below). In contrast, maturation is unlikely to explain our findings, given that false-positive findings were especially high for infants screened at term age as opposed to preterm age.

4.2.3 Gestational age and delivery circumstance

Although the majority of preterm births are spontaneous rather than medically indicated, the proportion of spontaneous births is greater at lower gestational ages [18 27]. As a result, we repeated our analyses with gestational age-based subgroups stratified by delivery circumstance. We observed slightly stronger associations for spontaneous PTB compared to medically indicated PTB within each gestational age group, though these differences were non-significant except for late PTB. Importantly, effect sizes were similar to the gestational age analysis, suggesting that the gestational age findings could not be attributed to the differential distribution of delivery circumstance. Our findings also remained largely unchanged following the stratification by corrected age at screening, except for moderate preterm births. Specifically, among infants screened at term-equivalent age, greater odds of false positive findings were observed in the context of indicated versus spontaneous deliveries. This may suggest that the strong association observed among moderate preterm infants screened at term age may be mostly attributable to medically indicated births, though present among both types of deliveries.

4.2.4 Effect of corrected age at screening

Across all of our analyses, we observed stronger associations for infants who were screened at term-equivalent age compared to those screened while still at a preterm age, particularly within the moderate PTB subgroup. This suggests that the presence of middle ear fluid, which is commonly resolved within hours of delivery and can result in false-positive newborn hearing screening findings [85], cannot explain this pattern of results. Instead, factors

that covary with longer hospital stays may be responsible, such as earlier gestational age at birth, obstetric complications, and/or antepartum complications. Newborn morbidities are another factor to consider, given that preterm infants who are screened and discharged at term-equivalent age are likely to be hospitalized for longer periods of time following birth compared to those born at equivalent gestational ages who are screened and discharged before term-equivalent age [86 87]. It is also important to note that some drugs used in NICU treatment and some characteristics of the NICU environment itself, such as high noise levels, may have ototoxic or neurodevelopmental effects [88]. Better understanding how these factors relate to false-positive findings, perhaps through the inclusion of medical record data, would be helpful to evaluating whether these findings are innocuous or have etiologic or prognostic significance.

4.2.5 Heterogeneity of moderate preterm birth

Our results also suggested that moderate preterm infants are a highly heterogeneous group warranting further study. The greatest difference between infants screened at a preterm age and those screened at term-equivalent age was within the moderate PTB subgroup, while effect sizes did not differ significantly from each other within the extreme and late PTB subgroups following stratification. Moderate preterm infants have been relatively understudied compared to late and extremely preterm infants, but some characteristics observed in this group may play a role in explaining our findings. One study assessing length of stay in infants born between 30–34 gestational weeks found that low birth weight for gestational age and nasal CPAP treatment were associated with longer lengths of stay, suggesting that developmental immaturity and pulmonary morbidities may contribute to longer length of stay for moderate preterm infants [89]. Other studies have also found that lower gestational ages within the moderate PTB range are associated with longer lengths of stay and greater weight gain before discharge [90]. Further, although most

preterm and low-birth-weight for gestational age infants meet conditions required for discharge before term-equivalent age, lower birth weights are associated with older corrected age at discharge [86]. Additional factors associated with prolonged hospitalization in moderate preterm infants include inadequate oral feeding, apnea, bradycardia, continued respiratory difficulties at 28 days, and delivery room resuscitation [91-93].

Another potential explanation for the heterogeneity in moderate PTB is the wide range of gestational ages that this category covered (28–34 weeks). Infants born at the earlier end of this range of gestational ages are known to generally require more medical intervention than those born closer to the late PTB range. For example, respiratory illness is more common in infants born at 29 weeks compared to those born at 33 weeks [91], and as described above, pulmonary morbidities may increase length of stay for moderate preterm infants. It is possible that the range of gestational ages chosen for this subgroup combined both infants who were more similar to extreme preterm infants and those who were more similar to late preterm infants. However, this would not explain why moderate preterm infants screened at a preterm age appeared to have a weaker association with false-positive results than late preterm infants screened at preterm or term age. Attempts to disentangle the impacts of gestational age at delivery and newborn morbidities on false-positive findings will be an important direction for future work.

4.3 Study limitations

4.3.1 Possible misclassification of delivery circumstance

One limitation of our analysis is the possibility of misclassification of delivery circumstance. [84]. Although the algorithm we used was validated using manual review of obstetric records, some variables used in the algorithm, such as premature rupture of membranes, are no longer incorporated in birth certificate files due to reliability and validity concerns [84 94

95]. Some evidence suggesting that delivery circumstance was misclassified in our data comes from the fact that the prevalence of medically indicated PTB was 40% in our sample, whereas other studies with more rigorous characterization of delivery circumstance report a prevalence of approximately 30% [22]. Thus, it is likely that a portion of the medically indicated deliveries in our sample are actually spontaneous, and this might have obscured differences between these groups in our analysis. Notwithstanding possible misclassification, our findings suggest that both types of delivery circumstance for PTB are more strongly associated with false positives than full-term births and that there may be a slightly stronger association for spontaneous PTB compared to medically indicated PTB. This latter observation is in particular need for replication within a study with more rigorous categorization of delivery circumstance.

4.3.2 Limitations in available data

Despite our large sample, we do not have detailed medical information on either infants or their parents. For example, we have limited information regarding medical conditions leading to preterm birth. We also do not have data on reasons for NICU admission, infant morbidities, or treatments received while in the NICU. As mentioned above, some medications used in NICU treatment and characteristics of the NICU environment, such as high noise levels, may have ototoxic effects [88]. Our analyses adjusted for NICU admission to try to account for these factors.

We also do not have the screening results for infants who were screened multiple times prior to discharge; our findings use the results of the final test conducted. However, using the results of this final test likely reduced residual confounding from factors known to be associated with temporary hearing loss in neonates, such as middle ear fluid, although ABRs may be less affected by these factors compared to screening using otoacoustic emissions [85]. We also

conducted a sensitivity analysis using chronological age at screening to address whether antepartum factors such as fluid or middle ear debris could further characterize our findings (data not shown) and found limited evidence for its impact.

We note that our analyses include infant siblings who are born to the same mother. This source of non-independence was not taken into account in our analyses, but other preliminary work using these data suggests minimal impact. In addition, our analyses do not account for birth hospital. This may be important to consider because: 1) ABR equipment calibration may differ from one hospital to the next, perhaps leading to false positive rates that are site-specific, and 2) births to the same mother may be more likely to take place in the same hospital. Taken together with the fact that preterm births can recur within the same woman, taking both sibling status and birth hospital into account is imperative to determining whether our findings are robust to these factors.

4.3.3 Small cell sizes

Although we had a large overall sample size, some cell sizes were relatively small in the stratified and sensitivity analyses (e.g., moderate spontaneous PTB screened at term-equivalent age), and thus may be underpowered. However, despite wide confidence intervals, the effect sizes for our most prominent findings are large and fall below significance thresholds. However, cell sizes were relatively large for moderate preterm infants screened at a preterm age, who did not differ significantly from full-term infants after adjustment for covariates. This finding is unlikely to be underpowered and supports the conclusion that moderate PTB represents a heterogeneous group of infants.

As for the analysis using stratification by chronological age (data not shown), we attempted to identify a threshold number of days that would allow for sufficient cell sizes while

still allowing for analysis of confounding due to testing close to the time of birth. However, there were very few infants screened within a few days of birth in some of the subgroups, particularly the extreme preterm subgroup. This makes it difficult to assess the effect of temporary hearing loss due to factors such as middle ear fluid or debris on false-positive findings in these infants, though it is unlikely to affect our findings within these groups, as temporary factors are more likely to be resolved the greater the amount of time elapsed before screening.

4.3.4 Multiple comparisons

We ran multiple analyses to address the study aims, raising the possibility that some of our findings were observed by chance. That said, this concern is somewhat assuaged by the consistency of findings observed. However, there remains the possibility that some of the results that we report are actually null, and thus, replication of our findings is needed.

4.4 Study strengths

A strength of our study is the very large sample size upon which our analyses are based. While most studies measuring perinatal brain development in the context of ABRs or neurodevelopmental disorders have small sample sizes that typically do not exceed a few hundred individuals, our sample consisted of 651,391 infants, giving us sufficient power to identify small differences between groups. In addition, our sample was generally representative of the population of Michigan live births between 2007–2015, with the exception of a slight overrepresentation of non-Hispanic White birthing people and underrepresentation of non-Hispanic Black birthing people in our analytic sample.

We also conducted several sensitivity analyses that support the robustness of our findings. As described above, we repeated all analyses stratified by corrected age at screening to investigate whether differences would still be observed between preterm and full-term infants

when both were assessed at the same corrected age and by chronological age at screening to assess residual confounding by temporary hearing loss due to antepartum factors. Through these analyses, we discovered marked heterogeneity within the moderate PTB subgroup, which should be further investigated. We also repeated analyses after excluding infants with congenital anomalies and those who were lost to follow-up and findings were unaffected in both analyses (Tables 5–6). Our study therefore represents a highly comprehensive investigation of preterm birth and its association between false-positive, ABR-based newborn hearing screening findings and provides an informative context for future work.

This study also addresses an important gap in the literature by evaluating the effect of gestational age and delivery circumstance on false-positive, ABR-based hearing screening results. Although many studies have been conducted looking at high-resolution ABR characteristics, false positives in ABR-based hearing screening have been relatively understudied even though ABR-based hearing screening is ubiquitous, inexpensive, and could easily be leveraged for early screening programs for neurodevelopmental disorders. Our study provides evidence that preterm birth is associated with false-positive, ABR-based hearing screening results and that the proportion of false positives differs across different gestational ages in a non-linear fashion and may differ between different delivery circumstances.

4.5 Directions for future research

Further research is needed on the effect of different delivery circumstances on the risk of false-positive, ABR-based hearing screening results, as our findings were unclear. This is because our results suggest a consistently stronger, though non-significant, association among spontaneous PTB compared to medically indicated PTB. In addition, there was potential for misclassification of delivery circumstance (see above). Our findings need to be replicated in

future studies using more rigorous classification of delivery circumstance and incorporate obstetric health information to further examine this issue.

The great heterogeneity identified within moderate PTB also warrants further investigation. When moderate PTB was stratified by corrected age at screening, infants who were screened at a preterm age did not differ significantly from full-term infants, but screening at term-equivalent age was strongly associated with false-positive, ABR-based hearing screening results. Further research is required to identify factors that may explain this difference, including whether delivery circumstance or factors for which it serves as a proxy play any role given that medically indicated births screened at term-equivalent age had the largest effect size.

Finally, further research is needed to investigate the association between false-positive, ABR-based hearing screening results among preterm infants and risk of neurodevelopmental disorder diagnosis to determine whether these false-positive results reflect relevant alterations in neurodevelopment. Although we did not have data on childhood diagnoses for the infants in our study, both preterm birth and neurodevelopmental disorders have been associated with alterations in ABR characteristics [76-81 83]. This study identified patterns in characteristics of preterm birth that are associated with false-positive, ABR-based hearing screening results. If these associations extend to later diagnosis of neurodevelopmental disorders, then existing ABR-based universal newborn hearing screening programs may inform early identification of at-risk infants, potentially allowing for earlier diagnosis and intervention.

APPENDIX

Figure 1: Example of an auditory brainstem response (ABR) waveform with clinically relevant waves labeled.

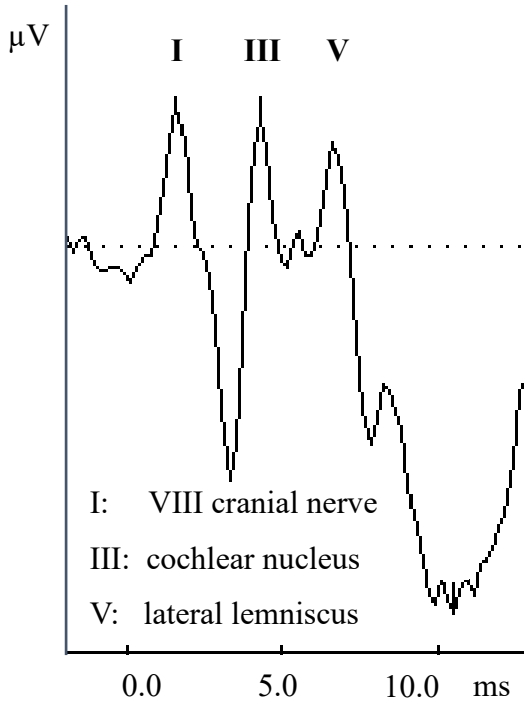

Figure 2: Analytic sample derivation.

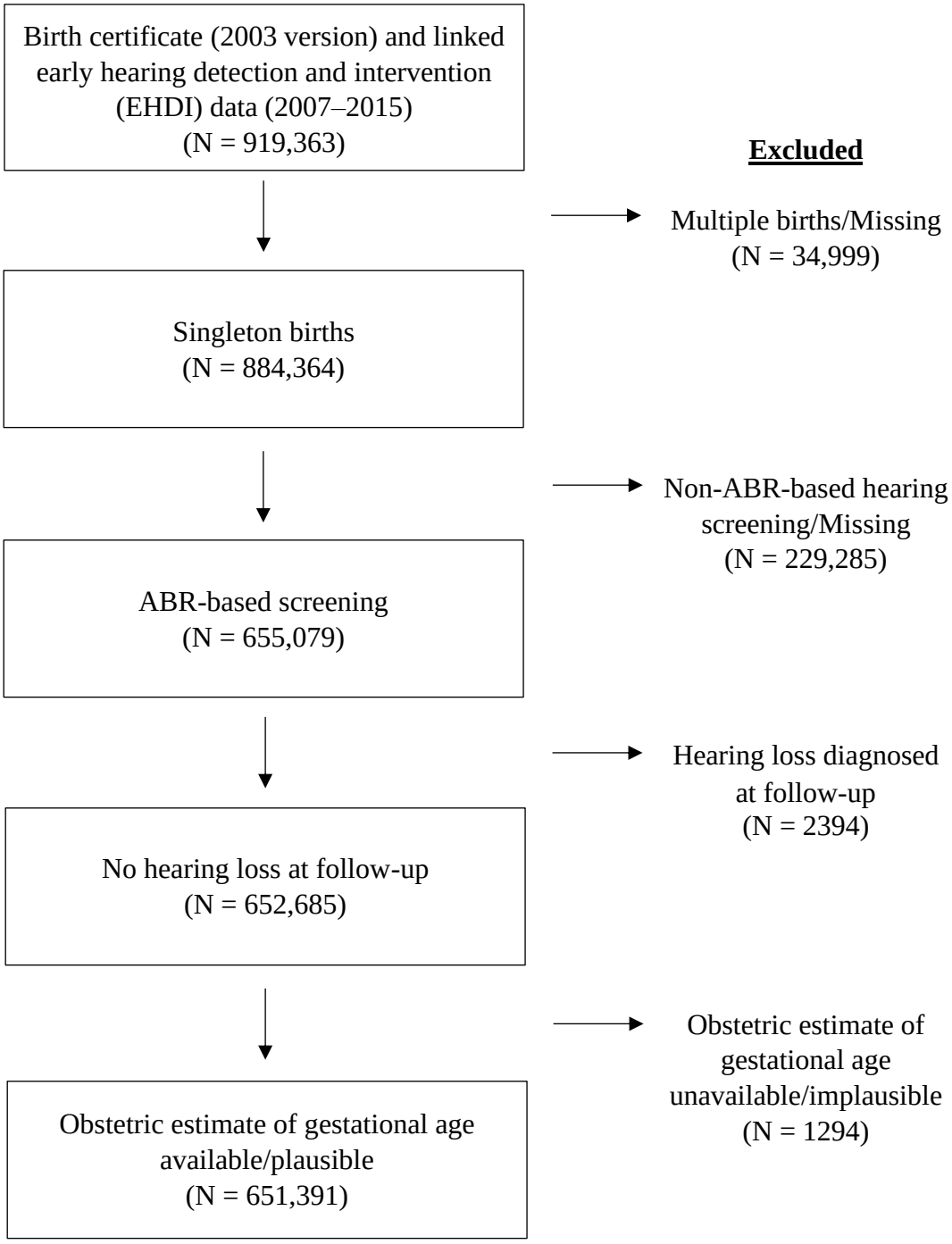

Table 1: *Maternal and infant characteristics among Michigan live births (2007–2015) and within the analytic sample.*

	Michigan live births **Max N = 919,363** **N (%)**	**Analytic sample** **Max N = 651,391** **N (%)**	**Type of variable**
Maternal sociodemographics			
Race/ethnicity			
Non-Hispanic White	632,582 (69)	472,056 (72)	Confounder
Non-Hispanic Black	168,793 (18)	95,471 (15)	
Hispanic	63,905 (7)	46,623 (7)	
Native American	3681 (<1)	2056 (<1)	
Asian/Pacific Islander	29,006 (3)	21,735 (3)	
Other	15,875 (2)	11,610 (2)	
Missing	5521 (1)	1840 (<1)	
Education			
Less than high school	130,295 (14)	83,187 (13)	Confounder
High school or equivalent	236,474 (26)	162,290 (25)	
Some college	294,501 (32)	212,395 (33)	
College degree	161,084 (18)	122,316 (19)	
Professional school	88,151 (10)	66,742 (10)	
Missing	8858 (1)	4461 (1)	
Age at delivery (years)			
<18	21,621 (2)	13,685 (2)	Confounder
18–25	274,893 (30)	187,065 (29)	
25–35	500,279 (54)	364,677 (56)	
≥35	119,172 (13)	85,960 (13)	
Missing	3398 (<1)	4 (0)	
Insurance status			
Private	492,456 (54)	356,811 (55)	Confounder
Medicaid	404,708 (44)	283,282 (43)	
Self-pay	9652 (1)	6190 (1)	
Other	6916 (1)	3706 (1)	
Missing	5631 (1)	1402 (<1)	
Smoking			
No	720,037 (78)	512,662 (79)	Confounder
Yes	191,719 (21)	135,335 (21)	
Missing	7607 (1)	3394 (1)	

Maternal smoking significant at $p < 0.05$. All other p-values significant at $p < 0.0001$.
PT: preterm, PTB: preterm birth, F/U: follow-up.

Table 1 (cont'd)

	Michigan live births Max N = 919,363 N (%)	Analytic sample Max N = 651,391 N (%)	Type of variable
Pregnancy/delivery characteristics			
Gestational age category			
Extreme PTB (<28 weeks)	4057 (<1)	1933 (<1)	Exposure
Moderate PTB (28–34 weeks)	17,644 (2)	9887 (2)	
Late PTB (34–36 weeks)	63,315 (7)	38,411 (6)	
Full-term (≥37 weeks)	829,043 (90)	601,160 (92)	
Missing	5304 (1)	0 (0)	
Delivery circumstance			
Full-term	829,043 (90)	601,160 (92)	Exposure
Spontaneous PTB	47,945 (5)	30,034 (5)	
Medically indicated PTB	37,055 (4)	20,190 (3)	
Missing	5320 (1)	7 (<1)	
Infant characteristics			
Sex			
Male	468,834 (51)	334,606 (51)	Confounder
Female	447,148 (49)	316,785 (49)	
Missing	3381 (<1)	0 (0)	
ABR-based hearing screening results			
True negatives	869,664 (95)	624,082 (96)	Outcome
True positives	2351 (<1)	0 (0)	
False negatives	618 (<1)	0 (0)	
False positives	39,479 (4)	27,309 (4)	
Missing	7251 (1)	0 (0)	
NICU admission			
No	846,386 (92)	606,051 (93)	Mediator
Yes	58,973 (6)	39,746 (6)	
Missing	14,004 (2)	5594 (1)	
Apgar score (5 min)			
<3	6209 (1)	4179 (1)	Mediator
4–6	17,142 (2)	10,957 (2)	
7–10	891,357 (97)	635,407 (98)	
Missing	4655 (1)	848 (<1)	
Congenital anomalies			
No	895,536 (97)	631,884 (97)	Confounder
Yes	23,827 (3)	19,507 (3)	
Missing	0 (0)	0 (0)	

Maternal smoking significant at $p < 0.05$. All other p-values significant at $p < 0.0001$.
PT: preterm, PTB: preterm birth, F/U: follow-up.

Table 1 (cont'd)

	Michigan live births Max N = 919,363 N (%)	Analytic sample Max N = 651,391 N (%)	Type of variable
Timing of ABR-based hearing screening			
Time from birth to ABR screening			
Same day	689,773 (75)	520,308 (80)	Mediator?
Within 2 days	138,636 (15)	79,061 (12)	
Within 3 days	20,740 (2)	12,303 (2)	
Between 4–13 days	36,917 (4)	24,345 (4)	
Between 14–27 days	11,763 (1)	7005 (1)	
After 28 days or more	12,265 (1)	7043 (1)	
Missing	9269 (1)	1326 (<1)	
Gestational age and age at screening			
Full-term birth	829,043 (90)	601,160 (92)	Mediator?
Late PTB, PT age	62,268 (7)	38,066 (6)	
Late PTB, term age	432 (<1)	254 (<1)	
Moderate PTB, PT age	16,851 (2)	9687 (1)	
Moderate PTB, term age	287 (<1)	156 (<1)	
Extreme PTB, PT age	2585 (<1)	1620 (<1)	
Extreme PTB, term age	509 (<1)	300 (<1)	
Missing	7388 (1)	148 (<1)	
Loss to follow-up			
Failed screen, F/U available	34,686 (4)	23,090 (4)	Confounder?
Failed screen, no F/U	7275 (1)	4219 (1)	
Missing screen, F/U available	2 (<1)	0 (0)	
Never screened	7106 (1)	0 (0)	
Missing (passed screen)	870,294 (95)	624,082 (96)	

Maternal smoking significant at $p < 0.05$. All other p-values significant at $p < 0.0001$.
PT: preterm, PTB: preterm birth, F/U: follow-up.

Table 2a: *Gestational age and its association with sociodemographic, pregnancy-, and birth-related characteristics in the analytic sample (N = 651,391).*

	Full-term (≥37 weeks)	**Late preterm (34–36 weeks)**	**Moderately preterm (28–34 weeks)**	**Extremely preterm (<28 weeks)**
	Max N = 601,160 N (%)	**Max N = 38,411 N (%)**	**Max N = 9887 N (%)**	**Max N = 1933 N (%)**
Maternal sociodemographics				
Race/ethnicity				
Non-Hispanic White	439,488 (73)	25,821 (67)	5830 (59)	917 (48)
Non-Hispanic Black	83,842 (14)	7862 (21)	2949 (30)	818 (42)
Hispanic	43,140 (7)	2709 (7)	640 (6)	134 (7)
Native American	1854 (<1)	156 (<1)	41 (<1)	5 (<1)
Asian/Pacific Islander	20,240 (3)	1210 (3)	251 (3)	34 (2)
Other	10,845 (2)	580 (2)	162 (2)	23 (1)
Education				
Less than high school	75,382 (13)	5712 (15)	1724 (18)	369 (19)
High school or equivalent	148,382 (25)	10,401 (27)	2932 (30)	575 (30)
Some college	196,118 (33)	12,552 (33)	3084 (31)	641 (34)
College degree	114,826 (19)	5942 (16)	1326 (14)	222 (12)
Professional degree	62,541 (10)	3420 (9)	679 (7)	102 (5)
Age at delivery (years)				
<18	12,390 (2)	908 (2)	304 (3)	83 (4)
18–25	172,016 (29)	11,307 (29)	3095 (31)	647 (34)
25–35	338,582 (56)	20,246 (53)	4916 (50)	933 (48)
≥35	78,169 (13)	5949 (16)	1572 (16)	270 (14)

All *p*-values significant at $p < 0.0001$. For corrected age at screening, *p*-value assessed for preterm only. Unable to assess *p*-value for time from birth to ABR screening due to sparsely populated cells. Percentages for loss to follow-up calculated using the total number of infants who failed screening within each subgroup.
PT: preterm, F/U: follow-up.

Table 2a (cont'd)

	Full-term (≥37 weeks) Max N = 601,160 N (%)	Late preterm (34–36 weeks) Max N = 38,411 N (%)	Moderately preterm (28–34 weeks) Max N = 9887 N (%)	Extremely preterm (<28 weeks) Max N = 1933 N (%)
Maternal sociodemographics (cont'd)				
Insurance status				
Private	332,062 (55)	19,393 (51)	4539 (46)	817 (42)
Medicaid	259,036 (43)	18,172 (47)	5046 (51)	1028 (53)
Self-pay	5455 (1)	475 (1)	198 (2)	62 (3)
Other	3344 (1)	262 (1)	82 (1)	18 (1)
Smoking				
No	474,766 (79)	29,128 (76)	7293 (74)	1475 (77)
Yes	123,369 (21)	9034 (24)	2497 (26)	435 (23)
Infant characteristics				
Sex				
Male	307,574 (51)	20,608 (54)	5394 (55)	1030 (53)
Female	293,586 (49)	17,803 (46)	4493 (45)	903 (47)
NICU admission				
No	575,492 (97)	27,863 (73)	2363 (24)	333 (17)
Yes	20,386 (3)	10,268 (27)	7497 (76)	1595 (83)
Apgar score (5 min)				
<3	3207 (1)	405 (1)	328 (3)	239 (12)
4–6	8090 (1)	1212 (3)	1075 (11)	580 (31)
7–10	589,208 (98)	36,696 (96)	8420 (86)	1083 (57)

All *p*-values significant at $p < 0.0001$. For corrected age at screening, *p*-value assessed for preterm only. Unable to assess *p*-value for time from birth to ABR screening due to sparsely populated cells. Percentages for loss to follow-up calculated using the total number of infants who failed screening within each subgroup.
PT: preterm, F/U: follow-up.

Table 2a (cont'd)

	Full-term (≥37 weeks) Max N = 601,160 N (%)	Late preterm (34–36 weeks) Max N = 38,411 N (%)	Moderately preterm (28–34 weeks) Max N = 9887 N (%)	Extremely preterm (<28 weeks) Max N = 1933 N (%)
Infant characteristics (cont'd)				
Congenital anomalies				
No	584,247 (97)	36,690 (96)	9197 (93)	1750 (91)
Yes	16,913 (3)	1721 (4)	690 (7)	183 (9)
Timing of ABR-based hearing screening				
Time from birth to ABR screening				
Same day	500,344 (83)	19637 (51)	315 (3)	12 (1)
Within 2 days	73,022 (12)	5892 (15)	147 (1)	0 (0)
Within 3 days	9814 (2)	2336 (6)	152 (2)	1 (<1)
Between 4–13 days	12,476 (2)	8826 (23)	3035 (31)	8 (<1)
Between 14–27 days	2431 (<1)	1277 (3)	3279 (33)	18 (1)
After 28 days or more	1895 (<1)	352 (1)	2915 (30)	1881 (98)
Corrected age at screening				
Screened at PT age	0 (0)	38,066 (99)	9687 (98)	1620 (84)
Screened at term age	601,160 (100)	254 (1)	156 (2)	300 (16)
Loss to follow-up				
Failed screen, F/U available	20,479 (85)	1948 (83)	403 (83)	260 (90)
Failed screen, no F/U	3698 (15)	413 (17)	80 (17)	28 (10)

All *p*-values significant at $p < 0.0001$. For corrected age at screening, *p*-value assessed for preterm only. Unable to assess *p*-value for time from birth to ABR screening due to sparsely populated cells. Percentages for loss to follow-up calculated using the total number of infants who failed screening within each subgroup.
PT: preterm, F/U: follow-up.

Table 2b: *Delivery circumstance and its association with sociodemographic, pregnancy-, and birth-related characteristics in the analytic sample (N = 651,391).*

	Full-term **Max N = 601,160** **N (%)**	**Spontaneous preterm** **Max N = 30,034** **N (%)**	**Medically indicated preterm** **Max N = 20,190** **N (%)**
Maternal sociodemographics			
Race/ethnicity			
Non-Hispanic White	439,488 (73)	18,891 (63)	13,674 (68)
Non-Hispanic Black	83,842 (14)	7379 (25)	4247 (21)
Hispanic	43,140 (7)	2192 (7)	1290 (6)
Native American	1854 (<1)	113 (<1)	89 (<1)
Asian/Pacific Islander	20,240 (3)	902 (3)	593 (3)
Other	10,845 (2)	507 (2)	258 (1)
Education			
Less than high school	75,382 (13)	5243 (18)	2560 (13)
High school or equivalent	148,382 (25)	8570 (29)	5337 (27)
Some college	196,118 (33)	9272 (31)	7003 (35)
College degree	114,826 (19)	4236 (14)	3253 (16)
Professional degree	62,541 (10)	2376 (8)	1825 (9)
Age at delivery (years)			
<18	12,390 (2)	943 (3)	352 (2)
18–25	172,016 (29)	10,097 (34)	4950 (25)
25–35	338,582 (56)	15,083 (50)	11,008 (55)
≥35	78,169 (13)	3911 (13)	3879 (19)
Insurance status			
Private	332,062 (55)	14,225 (47)	10,522 (52)
Medicaid	259,036 (43)	14,948 (50)	9294 (46)
Self-pay	5455 (1)	517 (2)	218 (1)
Other	3344 (1)	266 (1)	96 (<1)
Smoking			
No	474,766 (79)	22,345 (75)	15,547 (78)
Yes	123,369 (21)	7483 (25)	4482 (22)
Infant characteristics			
Sex			
Male	307,574 (51)	16,589 (55)	10,438 (52)
Female	293,586 (49)	13,445 (45)	9752 (48)

All *p*-values significant at $p < 0.0001$.

For corrected age at screening, *p*-value assessed for preterm only. Percentages for loss to follow-up calculated using the total number of infants who failed screening within each subgroup.

Missing: n = 7 (delivery circumstance).

PT: preterm, F/U: follow-up.

Table 2b (cont'd)

	Full-term Max N = 601,160 N (%)	Spontaneous preterm Max N = 30,034 N (%)	Medically indicated preterm Max N = 20,190 N (%)
Infant characteristics (cont'd)			
NICU admission			
No	575,492 (97)	19,225 (64)	11,330 (56)
Yes	20,386 (3)	10,631 (36)	8728 (44)
Apgar score (5 min)			
<3	3207 (1)	559 (2)	413 (2)
4–6	8090 (1)	1527 (5)	1340 (7)
7–10	589,208 (98)	27,825 (93)	18,367 (91)
Congenital anomalies			
No	584,247 (97)	28,657 (95)	18,973 (94)
Yes	16,913 (3)	1377 (5)	1217 (6)
Timing of ABR-based hearing screening			
Time from birth to ABR screening			
Same day	500,344 (77)	12,992 (43)	6970 (35)
Within 2 days	73,022 (11)	3569 (12)	2468 (12)
Within 3 days	9814 (2)	1383 (5)	1106 (5)
Between 4–13 days	12,476 (2)	6575 (22)	5293 (26)
Between 14–27 days	2431 (<1)	2514 (8)	2059 (10)
After 28 days or more	1895 (<1)	2927 (10)	2220 (11)
Corrected age at screening			
Screened at PT age	0 (0)	29,592 (99)	19,774 (98)
Screened at term age	601,160 (100)	368 (1)	342 (2)
Loss to follow-up			
Failed screen, F/U available	20,479 (85)	1645 (82)	966 (85)
Failed screen, no F/U	3698 (15)	354 (18)	167 (15)

All *p*-values significant at $p < 0.0001$.

For corrected age at screening, *p*-value assessed for preterm only. Percentages for loss to follow-up calculated using the total number of infants who failed screening within each subgroup.

Missing: n = 7 (delivery circumstance).

PT: preterm, F/U: follow-up.

Table 3: *Preterm birth and its association with false-positive, ABR-based hearing screening results by gestational age and delivery circumstance.*

	False positives **Total N = 27,309** **N (%)**	**True negatives (referent)** **Total N = 624,082** **N (%)**	**Unadjusted model** **OR (95% CI)**	**Adjusted model** **OR (95% CI)**	**Contrasts across PTB categories***
Aim #1: Preterm birth					
Preterm (<37 weeks)	3132 (6)	47,099 (94)	1.6 (1.5, 1.7)*	1.4 (1.3, 1.5)*	---
Full-term (≥37 weeks; referent)	24,177 (4)	576,983 (96)	---	---	
Aim #2a: Gestational age-based subgroups					
Extreme PTB (<28 weeks)	288 (15)	1645 (85)	4.2 (3.7, 4.7)*	3.3 (2.9, 3.8)*	Extreme > Late > Mod = FTB
Moderate PTB (28–34 weeks)	483 (5)	9404 (95)	1.2 (1.1, 1.3)*	1.0 (0.9, 1.1)	
Late PTB (34–36 weeks)	2361 (6)	36,050 (94)	1.6 (1.5, 1.7)*	1.4 (1.3, 1.5)*	
Full-term (≥37 weeks; referent)	24,177 (4)	576,983 (96)	---	---	
Aim #2b: Delivery circumstance-based subgroups					
Spontaneous PTB	1999 (7)	28,035 (93)	1.7 (1.6, 1.8)*	1.5 (1.4, 1.6)*	Spon = MI > FTB
Medically indicated PTB	1133 (6)	19,057 (94)	1.4 (1.3, 1.5)*	1.3 (1.2, 1.4)*	
Full-term birth (referent)	24,177 (4)	576,983 (96)	---	---	
Aim #2c: Gestational age subgroups stratified by delivery circumstance					
Extreme spontaneous	192 (16)	1038 (84)	4.4 (3.8, 5.2)*	3.5 (3.0, 4.0)*	Ex Spon = Ex MI > Late Spon > Late MI > Mod Spon = Mod MI = FTB
Extreme indicated	96 (14)	606 (86)	3.8 (3.1, 4.7)*	3.1 (2.5, 3.9)*	
Moderate spontaneous	289 (5)	5493 (95)	1.3 (1.1, 1.4)*	1.0 (0.9, 1.2)	
Moderate indicated	194 (5)	3910 (95)	1.2 (1.1, 1.4)*	1.0 (0.9, 1.2)	
Late spontaneous	1518 (7)	21,504 (93)	1.7 (1.6, 1.8)*	1.5 (1.4, 1.6)*	
Late indicated	843 (5)	14,541 (95)	1.4 (1.3, 1.5)*	1.3 (1.2, 1.4)*	
Full-term (referent)	24,177 (4)	576,983 (96)	---	---	

* $p < 0.05$. Contrasts across categories: > if $p < 0.05$, = if $p > 0.05$.

Adjusted model: Exposure variable + maternal race/ethnicity + maternal education + maternal age at delivery + maternal insurance + maternal smoking + congenital anomalies + infant sex.

PTB: preterm birth, FTB: full-term birth, MI: medically indicated, spon: spontaneous, ex: extreme, mod: moderate.

Table 4: *Preterm birth and its association with false-positive, ABR-based hearing screening results by gestational age and delivery circumstance, stratified by corrected age at screening.*

	False positives **Total N = 27,309** **N (%)**	**True negatives (referent)** **Total N = 624,082** **N (%)**	**Unadjusted model** **OR (95% CI)**	**Adjusted model** **OR (95% CI)**
Aim #1: Preterm birth				
Preterm screened at PT age	3021 (6)	46,352 (94)	1.6 (1.5, 1.7)*	1.4 (1.3, 1.5)*
Preterm screened at term age	86 (12)	624 (88)	3.3 (2.6, 4.1)*	2.7 (2.2, 3.4)*
Full-term (referent)	24,177 (4)	576,983 (96)	---	---
Aim #2a: Gestational age-based subgroups stratified by corrected age at screening				
Extreme PT, screened at PT age	242 (15)	1378 (85)	4.2 (3.7, 4.8)*	3.3 (2.9, 3.8)*
Extreme PT, screened at term age	46 (15)	254 (15)	4.3 (3.2, 5.9)*	3.5 (2.5, 4.8)*
Moderate PT, screened at PT age	453 (5)	9234 (95)	1.2 (1.1, 1.3)*	1.0 (0.9, 1.1)
Moderate PT, screened at term age	22 (14)	134 (86)	3.9 (2.5, 6.2)*	3.5 (2.2, 5.5)*
Late PT, screened at PT age	2326 (6)	35,740 (94)	1.6 (1.5, 1.7)*	1.4 (1.3, 1.5)*
Late PT, screened at term age	18 (7)	236 (93)	1.8 (1.1, 2.9)*	1.5 (0.9, 2.4)
Full-term (referent)	24,177 (4)	576,983 (96)	---	---
Aim #2b: Delivery circumstance-based subgroups stratified by corrected age at screening				
Spontaneous PT, screened at PT age	1940 (7)	27,652 (93)	1.7 (1.6, 1.8)*	1.5 (1.4, 1.6)*
Spontaneous PT, screened at term age	42 (11)	326 (89)	3.1 (2.2, 4.2)*	2.5 (1.8, 3.4)*
Medically indicated PT, screened at PT age	1081 (5)	18,693 (95)	1.4 (1.3, 1.5)*	1.3 (1.2, 1.4)*
Medically indicated PT, screened at term age	44 (13)	298 (87)	3.5 (2.6, 4.8)*	3.0 (2.2, 4.1)*
Full-term birth (referent)	24,177 (4)	576,983 (96)	---	---

* $p < 0.05$

Adjusted model: Exposure variable + maternal race/ethnicity + maternal education + maternal age at delivery + maternal insurance + maternal smoking + congenital anomalies + infant sex

PTB: preterm birth, PT: preterm.

Missing: n = 1326.

Table 4 (cont'd)

	False positives Total N = 27,309 N (%)	True negatives (referent) Total N = 624,082 N (%)	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)
Aim #2c: Gestational age subgroups stratified by delivery circumstance and corrected age at screening				
Extreme spontaneous, screened at PT age	166 (16)	890 (84)	4.5 (3.8, 5.3)*	3.5 (2.9, 4.1)*
Extreme spontaneous, screened at term age	26 (16)	141 (84)	4.4 (2.9, 6.7)*	3.4 (2.2, 5.3)*
Extreme indicated, screened at PT age	76 (13)	487 (87)	3.7 (2.9. 4.8)*	3.0 (2.3, 3.8)*
Extreme indicated, screened at term age	20 (15)	113 (85)	4.2 (2.6, 6.8)*	3.5 (2.2, 5.7)*
Moderate spontaneous, screened at PT age	278 (5)	5412 (95)	1.2 (1.1, 1.4)*	1.0 (0.9, 1.2)
Moderate spontaneous, screened at term age	7 (10)	60 (90)	2.8 (1.3, 6.1)*	2.4 (1.1, 5.2)*
Moderate indicated, screened at PT age	175 (4)	3821 (96)	1.1 (0.9, 1.3)	1.0 (0.8, 1.1)
Moderate indicated, screened at term age	15 (17)	74 (83)	4.8 (2.8, 8.4)*	4.4 (2.5, 7.7)*
Late spontaneous, screened at PT age	1496 (7)	21,350 (93)	1.7 (1.6, 1.8)*	1.5 (1.4, 1.6)*
Late spontaneous, screened at term age	9 (7)	125 (93)	1.7 (0.9, 3.4)	1.4 (0.7, 2.8)
Late indicated, screened at PT age	830 (5)	14,385 (95)	1.4 (1.3, 1.5)*	1.3 (1.2, 1.4)*
Late indicated, screened at term age	9 (8)	111 (92)	1.9 (1.0, 3.8)	1.5 (0.8, 3.2)
Full-term (referent)	24,177 (4)	576,983 (96)	---	---

* $p < 0.05$

Adjusted model: Exposure variable + maternal race/ethnicity + maternal education + maternal age at delivery + maternal insurance + maternal smoking + congenital anomalies + infant sex

PTB: preterm birth, PT: preterm.

Missing: n = 1326.

Table 5: *Preterm birth and its association with false-positive, ABR-based hearing screening results by gestational age and delivery circumstance in children without congenital anomalies.*

	False positives **Max N = 27,309 N (%)**	**True negatives (referent)** **Max N = 624,082 N (%)**	**Unadjusted model** **OR (95% CI)**	**Adjusted model** **OR (95% CI)**
Aim #1: Preterm birth				
Preterm (<37 weeks)	2885 (6)	44,752 (94)	1.6 (1.5, 1.6)*	1.4 (1.3, 1.5)*
Full-term (≥37 weeks; referent)	23,248 (4)	560,999 (96)	---	---
Aim #2a: Gestational age-based subgroups				
Extremely preterm (<28 weeks)	247 (14)	1503 (86)	4.0 (3.5, 4.5)*	3.2 (2.8, 3.7)*
Moderately preterm (28–34 weeks)	417 (5)	8780 (95)	1.2 (1.1, 1.3)*	1.0 (0.9, 1.1)
Late preterm (34–36 weeks)	2221 (6)	34,469 (94)	1.6 (1.5, 1.7)*	1.4 (1.3, 1.5)*
Full-term (≥37 weeks; referent)	23,248 (4)	560,999 (96)	---	---
Aim #2b: Delivery circumstance-based subgroups				
Spontaneous preterm birth	1853 (6)	26,804 (94)	1.7 (1.6, 1.8)*	1.5 (1.4, 1.6)*
Medically indicated preterm birth	1032 (5)	17,941 (95)	1.4 (1.3, 1.5)*	1.3 (1.2, 1.4)*
Full-term birth (referent)	23,248 (4)	560,999 (96)	---	---
Aim #2c: Gestational age subgroups stratified by delivery circumstance				
Extreme spontaneous	169 (15)	948 (85)	4.3 (3.7, 5.1)*	3.4 (2.9, 4.1)*
Extreme indicated	78 (12)	554 (88)	3.4 (2.7, 4.3)*	2.8 (2.2, 3.6)*
Moderate spontaneous	250 (5)	5172 (95)	1.2 (1.1, 1.3)*	1.0 (0.8, 1.1)
Moderate indicated	167 (4)	6307 (96)	1.1 (1.0, 1.3)	1.0 (0.8, 1.1)
Late spontaneous	1434 (6)	20,684 (94)	1.7 (1.6, 1.8)*	1.5 (1.4, 1.6)*
Late indicated	787 (5)	13,780 (95)	1.4 (1.3, 1.5)*	1.3 (1.2, 1.4)*
Full-term (referent)	23,248 (4)	560,999 (96)	---	---

* $p < 0.05$.

Adjusted model: Exposure variable + maternal race/ethnicity + maternal education + maternal age at delivery + maternal insurance + maternal smoking + infant sex.

Table 6: *Preterm birth and its association with false-positive, ABR-based hearing screening results by gestational age and delivery circumstance in children who were not lost to follow-up*

	False positives **Max N = 23,309** **N (%)**	**True negatives (referent)** **Max N = 624,082** **N (%)**	**Unadjusted model** **OR (95% CI)**	**Adjusted model** **OR (95% CI)**
Aim #1: Preterm birth				
Preterm (<37 weeks)	2611 (5)	47,099 (95)	1.6 (1.5, 1.7)*	1.4 (1.3, 1.5)*
Full-term (≥37 weeks; referent)	20,479 (3)	576,983 (97)	---	---
Aim #2a: Gestational age-based subgroups				
Extremely preterm (<28 weeks)	260 (14)	1645 (86)	4.5 (3.9, 5.1)*	3.7 (3.2, 4.2)*
Moderately preterm (28–34 weeks)	403 (4)	9404 (96)	1.2 (1.1, 1.3)*	1.0 (0.9, 1.2)
Late preterm (34–36 weeks)	1948 (5)	36,050 (95)	1.5 (1.4, 1.6)*	1.4 (1.3, 1.5)*
Full-term (≥37 weeks; referent)	20,479 (3)	576,983 (97)	---	---
Aim #2b: Delivery circumstance-based subgroups				
Spontaneous preterm birth	1645 (6)	28,035 (94)	1.7 (1.6, 1.5)*	1.5 (1.4, 1.6)*
Medically indicated preterm birth	966 (5)	19,057 (95)	1.4 (1.3, 1.5)*	1.3 (1.2, 1.4)*
Full-term birth (referent)	20,479 (3)	576,983 (97)	---	---
Aim #2c: Gestational age subgroups stratified by delivery circumstance				
Extreme spontaneous	172 (14)	1038 (86)	4.7 (4.6, 5.5)*	3.8 (3.2, 4.5)*
Extreme indicated	88 (13)	606 (87)	4.1 (3.3, 5.1)*	3.4 (2.7, 4.3)*
Moderate spontaneous	243 (4)	5493 (96)	1.2 (1.1, 1.4)*	1.0 (0.9, 1.2)
Moderate indicated	160 (4)	3910 (96)	1.2 (1.0, 1.4)	1.0 (0.8, 1.2)
Late spontaneous	1230 (5)	21,504 (95)	1.6 (1.5, 1.7)*	1.5 (1.4, 1.6)*
Late indicated	718 (5)	14,541 (95)	1.4 (1.3, 1.5)*	1.3 (1.2, 1.4)*
Full-term (referent)	20,479 (3)	576,983 (97)	---	---

* $p < 0.05$.

Adjusted model: Exposure variable + maternal race/ethnicity + maternal education + maternal age at delivery + maternal insurance + maternal smoking + infant sex.

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