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Published in final edited form as:

Ear Hear. 2020 ; 41(5): 1208–1214. doi:10.1097/AUD.0000000000000838.

Birth Weight and Adult-Onset Hearing Loss

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Abstract

Objectives: Among low birth weight infants, exposure to stress or under-nutrition in utero may adversely affect cochlear development. As cochlear reserve declines, the risk of hearing loss may increase with age. While low birth weight is associated with a higher risk of neonatal hearing loss, our objective was to examine whether birth weight was associated with adult-onset, self-reported hearing loss in the Nurses' Health Studies (NHS) I and II (n=113,130).

Design: We used Cox proportional hazards regression to prospectively examine whether birth weight, as well as gestational age at birth, are associated with adult-onset hearing loss. Participants reported their birth weight in 1992 in NHS I and 1991 in NHS II. Mothers of NHS II participants reported gestational age at birth in a sub-study (n=28,590). The primary outcome was adult-onset, self-reported moderate or greater hearing loss, based on questionnaires administered in 2012/2016 in NHS I and 2009/2013 in NHS II.

Results: Our results suggested a higher risk of hearing loss among those with birth weight <5.5 lbs compared with birth weight 7 to <8.5 lbs [pooled multivariable-adjusted hazard ratio (MVHR) 1.14, 95% CI 1.04, 1.23; P-trend 0.01]. Additionally, participants with gestational age at birth ≥42 weeks had a higher risk of hearing loss, compared with gestational age 38 to <42 weeks [MVHR 1.33, 95% CI 1.06, 1.65].

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Conclusion: Birth weight <5.5 lbs was independently associated with higher risk of self-reported, adult-onset hearing loss. In addition, gestational age at birth ≥42 weeks was also associated with higher risk.

Keywords

birth weight; gestational age; hearing loss; Nurses' Health Studies

INTRODUCTION

Hearing loss is a common and debilitating chronic health condition that has been linked to depression (Huang et al. 2010), dementia (Livingston et al. 2017), and increased mortality (Feeny et al. 2012). Data suggest that over half of adults in the United States have bilateral hearing loss by age 60 (Agrawal, Platz, & Niparko, 2008). Identifying risk factors for hearing loss and determining which adults warrant closer monitoring are major public health goals.

Birth weight has been associated with the development of a number of conditions in adult life, including obesity, hypertension, and diabetes mellitus. For instance, in the Nurses' Health Studies (NHS) (Curhan et al., 1996a) and the Health Professionals Follow-up Study (Curhan et al. 1996b), low birth weight (LBW) was independently associated with an increased risk of adult-onset hypertension and diabetes, while birth weight >10 pounds (lbs) was associated with an increased risk of obesity.

Studies have also linked very LBW to hearing loss in preterm infants (Kim et al. 2017; Wroblewska-Seniuk et al. 2017). Among LBW infants, fetal exposure to high levels of stress hormones or under-nutrition may lead to alterations in the cochlear microcirculation; as cochlear reserve declines with aging, these changes may lead to hearing loss later in life (Barker 1998). Prolonged pregnancy (gestational age >42 weeks) has also been associated with physiologic stress and uteroplacental insufficiency (Olesen, Westergaard, & Olsen 2003), which could adversely influence auditory system development.

Studies examining the association between LBW and prevalent hearing loss are largely cross-sectional, impeding the ability to assess the temporality of the association (Sayer et al. 1998, Barrenäs et al. 2005). We therefore examined the relation between LBW and incident adult-onset hearing loss in two large cohorts, the NHS I and II ((n=113,130). A secondary aim was to assess whether gestational age at birth among participants in NHS II was associated with hearing loss in adulthood.

MATERIALS AND METHODS

Study Participants

The Conservation of Hearing Study examines risk factors for hearing loss among participants in the Nurses' Health Studies. The NHS I and NHS II are prospective cohort studies exploring risk factors for chronic disease in women (Colditz et al. 1986; Bao et al. 2016). The NHS I was established in 1976 when 121,700 married, female registered nurses aged 30–55 years answered the baseline questionnaire. The NHS II is a distinct cohort of

116,430 female participants aged 25–42 years at baseline in 1989. The original purpose of the NHS was to explore contraceptive methods, smoking, cancer, and heart disease (Stampfer et al. 1985; Stampfer et al. 1988), but the focus has now expanded to a number of chronic diseases, lifestyle factors, and behaviors. Women have been followed by biennial questionnaires eliciting information on diet, lifestyle, and various health outcomes, with a follow-up rate of more than 90% of the eligible person-time.

We excluded women who were either missing data on birth weight, or answered "not sure" on NHS I questionnaires (n=19, 845) or "unknown" in NHS II questionnaires (n=13,461). We further limited the analysis to those women who provided information on their hearing and age of onset of change in hearing (if applicable) on the 2012 or 2016 (NHS I), or 2009 or 2013 (NHS II) questionnaires. We excluded women who reported a hearing problem that began before the baseline, 1980 (NHS I) or 1991 (NHS II), or who did not report age of onset of hearing loss. We also excluded those women who reported a history of cancer other than non-melanoma skin cancer due to possible exposure to ototoxic chemotherapeutic agents. Excluded women in NHS I (n=24,732) and NHS II (n=16,266) did not differ significantly in their baseline characteristics when compared with those women included in the analyses in NHS I and II (n=113,130) (eTable 1).

Ascertainment of Birth Weight and Preterm Birth

Women were asked about their birth weight in 1992 in NHS I (response options: not sure, <5 pounds lbs, 5-5.5 lbs, 5.6-7 lbs, 7.1-8.5 lbs, 8.6-10 lbs, and ≥10 lbs). Women in NHS II were asked about their birth weight in 1991 (response options: unknown, <5.5 lbs, 5.5-6.9 lbs, 7-8.4 lbs, 8.5-9.9 lbs, and ≥10 lbs). In both cohorts, participants were asked if they were born full-term or 2+ weeks preterm. Several validation studies have previously demonstrated the reliability of self-report of birth weight and preterm birth (Tomeo et al. 1999, Sou et al. 2006).

Gestational Age

In 2001, a sub-study collected information on demographics, health, and pregnancy-related information from the mothers of NHS I and II participants (Michels et al. 2007). A total of 39,904 Mothers' Questionnaires were completed in 2001 and 2002. The majority of mothers (n=35,830; 90%) had daughters who were participants in NHS II. Because of the small numbers of mothers in the NHS I sub-study, we limited all analyses to the data provided by mothers of participants in NHS II (n=28,590).

Mothers were asked if they smoked cigarettes, received prenatal care, had an infection, were hospitalized, or had preeclampsia/eclampsia during pregnancy. They were also asked about maternal age at participant's birth, and weight gain during pregnancy (response options: <10 lbs, 10 to <15 lbs, 15 to <20 lbs, 20 to <30 lbs, 30 to <40 lbs, and ≥40 lbs). Women were asked about singleton versus twin pregnancies, and if they had ever been diagnosed with gestational diabetes by a physician.

We used information from the Mothers' Questionnaires to examine gestational age (GA) at birth, as this refined exposure measure could be more informative than the simpler distinction of pre- or post-term birth. Both preterm and post-term pregnancies have been associated with a number of adverse health outcomes in the neonatal period and later in life (Caughey & Musci 2004; Gibson 2007; Middleton, Shepherd, & Crowther 2018). GA was derived based on the mothers' report of due date and the birth date of the participant, and was categorized as <38 weeks, 38 to <42 weeks, and ≥42 weeks in the questionnaires.

Ascertainment of Hearing Loss

The primary outcome was self-reported moderate or greater hearing loss. NHS I participants were asked in 2012, "Do you have a hearing problem?" (response options: none, mild, moderate, severe), and if so, at what age a change in hearing was first noticed. In 2016, NHS I participants were asked to describe their hearing (response options: excellent, good, a little trouble hearing, moderate trouble hearing, a lot of trouble hearing, deaf). For NHS II, the 2009 questionnaire asked, "Do you have a hearing problem?" (no, mild, moderate, severe), and "At what age did you first notice a change in your hearing?" On the 2013 questionnaire, NHS II participants were asked, "Which best describes your hearing?" (excellent, good, a little hearing trouble, moderate hearing trouble, deaf), and "Have you noticed a change in your hearing?" If the response was "Yes," they were asked, "At what age did you first notice a change in your hearing?"

We chose *a priori* to examine the incidence of self-reported moderate or greater hearing loss to minimize misclassification bias, as the likelihood of over- or underestimating degree of hearing loss may be higher among those reporting "mild" hearing loss. The use of questionnaires to assess hearing loss has been found to be reliable in previous studies (Ferrite, Santana, & Marshall 2011; Schow, Smedley, & Longhurst 1990), and has been effective in detecting associations in these and similar cohorts (Nondahl et al. 1998; Gomez et al. 2001; Curhan et al. 2004; Ferrite et al. 2011). In a validation study of self-reported hearing loss compared with audiometrically measured hearing loss, the sensitivity of a single question to detect moderate or greater hearing loss as measured by audiometry (better ear pure tone average [PTA] 0.5,1,2,4 kilohertz [kHz] >40 decibels [dB]) among women aged less than 70 years was 95% and the specificity was 65% (Sindhusake et al. 2001).

Ascertainment of Covariates

We considered factors that have been previously associated with hearing loss, including age, race, tinnitus (obtained from the 2012 NHS I and 2009 NHS II questionnaires), body mass index (Curhan et al. 2013), waist circumference (ascertained in 1986 and 1996 in NHS I and 1993 and 2005 in NHS II) (Curhan et al. 2013), menopause and age at menopause (Curhan et al. 2017), physical activity level (Curhan et al. 2013), diet (Curhan, Wang, & Eavey et al. 2018), alcohol consumption (Curhan et al. 2011), smoking (Cruickshanks et al. 1998), hypertension (Lin et al. 2016), diabetes mellitus (either type 1 or type 2) (Kim et al. 2017), and use of non-steroidal anti-inflammatory agents, aspirin, and acetaminophen (Curhan et al. 2012; Lin et al. 2017). Dietary data were derived from validated semi-quantitative food frequency questionnaires, which are sent to participants every 4 years. We used information from these questionnaires to calculate a score that measured adherence to the Alternate Mediterranean diet (AMED), a healthful dietary pattern (Fung et al. 2009), which was inversely associated with risk of hearing loss in NHS II (Curhan, Wang, & Eavey et al.

2018). Physical activity was assessed in quintiles (metabolic equivalents/week), and smoking was categorized as never smoker, past smoker, and current smoker.

Using responses from the Mothers' Questionnaire, we also assessed whether hospitalizations, preeclampsia/eclampsia, infection, smoking, weight gain during pregnancy, a diagnosis of gestational diabetes during pregnancy, or maternal age at participant's birth confounded the relation between birth weight and hearing loss in NHS II. We examined these maternal factors because they may negatively impact uteroplacental blood flow (Goldenberg & Culhane 2007; Meler et al. 2010), and placental insufficiency has been associated with lower birth weight and intrauterine growth restriction.

Statistical Analysis

Cox proportional hazards regression with age as the time scale was used to estimate the hazard ratio (HR) of adult-onset moderate or greater hearing loss (Cox 1972), using information collected before the reported onset of hearing loss. Person-time of follow-up was allocated according to exposure status at the start of each follow-up period, and time-varying covariates were updated as well using the counting process approach. In NHS I, this was calculated from the date of return of the 1980 questionnaire until the date of self-reported hearing loss, end of follow-up in 2016, or loss to follow-up (<5% in NHS). In NHS II, person-time of follow-up was calculated from the date of return of the 1991 questionnaire until the date of self-reported hearing loss or end of follow-up in 2013. Participants were censored at the reported onset of hearing loss or new cancer diagnosis, due to possible exposure to ototoxic chemotherapeutic agents.

SAS PROC PHREG was used for all analyses and the Anderson-Gill data structure was used to handle time-varying covariates efficiently (Therneau 1997). In the Anderson-Gill data structure, a new data record is created for every questionnaire cycle at which a participant was at risk, with covariates set to their values at the time the questionnaire was returned.

To control as finely as possible for confounding by age, calendar time and any possible two-way interactions between these two time scales, we stratified the analysis jointly by age at start of follow-up and calendar year of the current questionnaire cycle. The time scale for the analysis was then measured since the start of the current questionnaire cycle, which is equivalent to age because of the way we structured the data and formulate the model for analysis. Departures from the proportional hazards assumption, i.e. effect modification by age or calendar time, was tested by likelihood ratio tests comparing models with and without the interaction terms of age or calendar time by exposure. The interaction of each confounder was also tested as a function of survival time and included in the model. The proportional hazards assumption was not violated for any of the variables included in the model.

In the primary analysis, birth weight 7 to <8.5 lbs was the referent group. We investigated the risk of moderate or greater hearing loss separately in each cohort. We then used a meta-analysis macro (Smith-Warner, Spiegelman, & Ritz et al. 2006; Hertzmark & Spiegelman 2010) to obtain the pooled parameter estimates and HRs after controlling for the same covariates in both cohorts (we collapsed the <5 and 5 to < 5.5 lb categories in NHS I to <5.5

lbs in order to pool the results across NHS I and NHS II). Women who reported mild hearing loss on the 2012 NHS I questionnaire or 2009 NHS II questionnaire were skipped for that time period and reentered the analysis as a case if they subsequently reported moderate or greater hearing loss on the 2013/2016 questionnaires. To examine possible interactions, we stratified by self-reported preterm birth in each cohort (yes vs. no) and by age<60 and ≥60. For the stratified analyses, we collapsed birth weight categories into <5.5 lbs, 5.5 to <7 lbs, and ≥7 lbs due to small numbers of cases.

In NHS II, we examined whether lack of prenatal care, hospitalization, infection, maternal age at participant's birth, weight gain, or preeclampsia/eclampsia during the mother's pregnancy with the participant influenced the MVHR.

For the analysis of GA at birth and risk of adult onset hearing loss, GA was categorized in the questionnaires as <38 weeks, 38 to <42 weeks (referent group) and ≥42 weeks. We examined whether the MVHR was influenced by the addition of birth weight to the models.

We considered 15 candidate variables that based on background knowledge of clinically-relevant variables associated with birth weight and hearing loss; covariates were selected by performing backwards selection with a significance criterion of p=0.10. In the primary analysis of birth weight and hearing loss, we adjusted for waist circumference, physical activity, race, hypertension, diabetes mellitus, tinnitus, and AMED score. After determining that the relation between birth weight and hearing loss was neither quadratic nor J-shaped, a linear trend across birth weight categories was evaluated by assigning a median value to each category, including the extreme categories, and modeling this variable as a continuous variable (Li et al. 2015). For the extreme categories of <5.5 and ≥8.5, we used 5.2 lbs and 9.2 pounds, respectively, for the p-for trend calculations.

Unadjusted Kaplan-Meier curves were generated using %LEFTTRUNC SAS macro in the combined cohort, as well as individual cohorts, and compared using the log-rank test (Kaplan & Meier 1958).

P-values are all two-sided. A p-value <0.05 was used as the threshold for significance. SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

This study was approved by the Partners Healthcare Institutional Review Board.

RESULTS

Baseline Characteristics

The baseline characteristics of participants according to category of birth weight in NHS I and II are shown in Table 1. In both cohorts, participants with the lowest birth weight were more likely to have been born 2 or more weeks preterm. Mean age at baseline in 43.7 years (SD 6.5) in NHS I and 36.2 years (SD 4.7) in NHS II.

In NHS II, women with lower birth weight (<5.5 lbs) were more likely to have mothers who were hospitalized, smoked, or had preeclampsia/eclampsia during pregnancy, compared with women with a birth weight 7 to <8.5 lbs (Table 2). Women with lower birth weight were also more likely to have mothers who gained <15 lbs during pregnancy compared with women with a birth weight 7 to <8.5 lbs.

Birth Weight

During 2,718,281 person-years of follow-up, there were 10,885 cases of adult-onset moderate or greater hearing loss reported. Unadjusted Kaplan-Meier curves are shown in Supplementary Figures 1 through 3 (log-rank test, p-value <0.0001 for the combined cohort and individual cohorts). In the pooled analysis, there was a higher MV-adjusted risk of adult-onset hearing loss among those in the lowest birth weight category (<5.5 lbs) compared with those with birth weight 7 to <8.5 lbs [MVHR 1.14, 95% 1.04, 1.23] (Table 3). In the cohort-specific analyses, there was a higher MV-adjusted risk of moderate or greater hearing loss in women with birth weights <5 lbs in NHS I and <5.5 lbs in NHS II compared with those participants with birth weights between 7 and <8.5 lbs (eTable 2). The multivariable-adjusted HRs for LBW in NHS I (<5 lbs) and NHS II (<5.5 lbs) were not materially changed with the addition of age at menopause to the models. Further adjustment for preterm birth, gestational age at birth, and maternal risk factors did not materially change the results (results not shown). When the baseline for the NHS I analysis was changed from 1980 to 1992 (the year participants were asked about their birth weight), the MVHR for moderate or greater hearing loss among those women with birth weight < 5 lbs was unchanged [1.13, 95% 1.00,1.26].

There was no significant interaction between preterm birth and birthweight, nor was there a significant interaction between birth weight and age <60 versus ≥60 years. The association between birth weight and risk of hearing loss did not vary by full-term versus preterm birth (P-interaction = 0.11 (NHS I); P-interaction=0.33 (NHS II) (eTable 3) or by age <60 versus ≥60 years (P-interaction=0.28 (NHS I); P-interaction=0.68 (NHS II)) (eTable 4).

Gestational Age

Among those participants with gestational age at birth ≥42 weeks, there was a higher risk of adult-onset moderate or greater hearing loss compared with those with gestational age between 38 to <42 weeks (MVHR 1.33, 95% CI 1.06, 1.65) (Table 4). Further adjustment for birth weight did not materially change the results.

DISCUSSION

In this longitudinal study of 113,130 women, we found a slightly higher risk of adult-onset, self-reported moderate or greater hearing loss among participants with LBW. The association between birth weight and adult-onset hearing loss did not differ between those who were and were not born preterm. Furthermore, the birth weight HRs did not change after adjusting for pregnancy-related maternal factors. NHS II participants with gestational age at birth ≥42 weeks had a greater risk of adult-onset moderate or greater hearing loss.

The association between birth weight and adult-onset hearing loss has not been well-studied. Among LBW infants, the prevalence of sensorineural hearing loss is higher than in the general newborn population, likely due to complications of LBW, including hypoxia, infection, ototoxic medications, and hyperbilirubinemia (Haupt, Scheibe, & Ludwig 1993; Lin et al.2018). Many studies have examined the association of LBW and prevalent hearing loss among children and adolescents, thus it is uncertain when the hearing loss began (Sayer et al. 1998; Nafstad et al. 2002; Barrenäs et al. 2005; Dawes et al. 2015). In a Norwegian study of children and adolescents, the odds of hearing impairment was higher for birth weight <1500 grams (g) and lower for birth weight >4499 g, when compared with a birth weight between 3000 and 3499 g (Nafstad et al. 2002). This was similar to the results from another study using National Health Examination Survey data (Hoffman et al. 2018).

It is possible that the adverse influence of LBW on the auditory system may also encompass subclinical pathologic changes that do not manifest until later in life. In our analysis, we found a modestly higher risk of adult-onset moderate or greater hearing loss among those with LBW. The higher risk of hearing loss was independent of hypertension, diabetes, and waist circumference, and a number of maternal factors. It is not clear if the higher risk of hearing loss is attributable to pre- or post-natal factors, but it is possible that it is a combination of both. Prior studies show that birth weight has been associated with the development in adulthood of other chronic health conditions, including hypertension, diabetes mellitus, and obesity, all of which have been found to be risk factors for hearing loss in prior studies (Curhan et al.2013; Lin et al. 2016; M. Kim et al. 2017). Notably, after adjusting for these risk factors, the association between LBW and adult-onset hearing loss was not appreciably changed. The association with adult-onset chronic disease may be attributable to fluctuations in fetal blood flow or hormone levels, thereby leading to abnormal development of the organ systems responsible for blood pressure regulation and glucose control (Barker 1992; Brenner & Chertow 1994; Curhan et al. 1996). It is possible that adult-onset hearing loss may occur by similar mechanisms.

Early exposure to adverse conditions, such as hypoxia, stress, and under-nutrition, may result in poor health outcomes later in life, a phenomenon described as “fetal programming” or the “thrifty phenotype hypothesis” (Barker DJP 1998; Barrenäs et al. 2005). Furthermore, adequate blood supply to the cochlea is essential for maintaining the endocochlear potential, ion transport, and endolymphatic balance (Shi 2011). Disruptions in the vasculature in utero could lead to disturbances in the cochlear microcirculation and endothelial dysfunction, thereby predisposing to hearing loss later in life due to reduced cochlear reserve. Even though we adjusted for hypertension, changes to the cochlear microcirculation distinct from hypertension or macrovascular disease can still occur (Shi, 2011). With aging, degeneration of cochlear synapses and loss of hair cells may deplete cochlear reserve, increasing susceptibility to hearing loss (Kujawa & Liberman 2015). Alternatively, there may be early alterations in gene expression affecting auditory function in adulthood (Provenzano & Domann 2007). It is therefore plausible that microvascular disease, aging, and genetic and hormonal factors may collectively predispose to adult-onset hearing loss as cochlear reserve is depleted.

We also found that longer GA at birth (≥42 weeks) was associated with a higher risk of adult-onset moderate or greater hearing loss. Post-term pregnancy is associated with an increased risk of neonatal morbidity and mortality, across all categories of birth weight (Bruckner, Cheng, & Caughey 2008). Infants born after 41 weeks of gestation have lower

Apgar scores, and a higher risk of macrosomia and neonatal encephalopathy, which may contribute to a higher risk of congenital hearing loss (Spellacy et al. 1985; Badawi et al. 1998). Nevertheless, these associations do not explain our finding of a higher risk of adult-onset hearing loss, which was unexpected and warrants further investigation. GA >42 weeks has been associated with asphyxia, which could also compromise vascular supply to the cochlea (Olesen et al. 2003). Much like LBW, fetal programming could increase susceptibility to hearing loss later in life as cochlear reserve declines.

To our knowledge, this is the first longitudinal study to examine birth weight and gestational age at birth and the risk of adult-onset hearing loss. Data obtained from NHS I and NHS II are highly reliable, with follow-up rates >90% of the eligible person-time. However, this study has limitations. Hearing loss was self-reported. While pure-tone audiometry is considered the gold standard for evaluating hearing loss, self-reported hearing loss is a reliable indicator of hearing loss (Gomez et al. 2001; Ferrite et al. 2011; Kamil, Genther, & Lin 2015). Several prior studies conducted in NHS I and NHS II have identified important risk factors for self-reported hearing loss (Curhan et al. 2011; Curhan et al. 2012; Curhan et al. 2015; Lin et al. 2016). Furthermore, by examining moderate or greater hearing loss as the primary outcome, we attempted to minimize misclassification. The study consisted of mostly non-Hispanic white women, which may limit the generalizability. We were also unable to examine the association among individuals who were born small for gestational age, as well as the possible influence of intrauterine growth retardation, and subsequent risk of hearing loss. This relation merits further study.

Based on the findings from this large prospective study, birth weight <5.5 lbs and gestational age ≥42 weeks are associated with a higher risk of adult-onset, self-reported hearing loss. While a relation between LBW and higher risk of childhood hearing loss has been demonstrated, LBW may also be associated with hearing decline later in life. These findings could have important implications for screening individuals for hearing loss beyond childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors would like to thank the participants of the Nurses' Health Studies for their ongoing contributions.

Sources of Support:

This work was supported by the National Institute on Deafness and Other Communication Disorders at the National Institute of Health (1F32DC017342 to SG and DC091417 to GCC), and the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institute of Health (DK091417 to GCC). NHS I and NHS II are supported by the following grants from the National Institute of Health: UM1CA186107 and UM1CA17626.

Conflicts of Interest:

SG: none

MW: none

BH: none

SGC: consultant for Decibel Therapeutics

GCC: grant support from Shoebox Audiometry; consultant for Allena Pharmaceuticals (urine oxalate); consultant for Shire (hypoparathyroidism); consultant for AstraZeneca (hyperkalemia)

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Table 1:

Baseline Characteristics for NHS I (1980) and NHS II (1991) Participants According to Birth Weight Category

	Birth Weight in NHS I					Birth Weight in NHS II			
	<5 lbs (n=1,875)	5 to <5.5 lbs (n=2,752)	5.5 to <6.9 lbs (n=13,747)	7 to <8.5 lbs (n=19,938)	≥ 8.5 lbs (n=5,576)	<5.5 lbs (n=5,279)	5.5 to <6.9 lbs (n=20,986)	7 to <8.5 lbs (n=33,711)	≥ 8.5 lbs (n=9,266)
Characteristic									
Age, yrs	44.1 (6.4)	42.8 (6.2)	43.4 (6.4)	43.6 (6.5)	44.8 (6.6)	36.7 (4.6)	36.2 (4.7)	36.2 (4.7)	35.8 (4.7)
BMI, kg/m^2	24.1 (4.4)	23.5 (4.0)	23.6 (4.0)	24.0 (4.1)	24.6 (4.5)	24.6 (5.4)	24.3 (5.2)	24.5 (5.2)	25.0 (5.4)
***Waist Circumference, cm**	77.4 (11.0)	76.1 (10.3)	76.2 (10.1)	77.6 (10.5)	78.9 (11.1)	77.8 (13.0)	77.1 (12.4)	78.1 (12.5)	79.3 (13.5)
White Race, %	94.1	94.0	94.8	95.7	95.1	94.3	94.0	95.8	95.9
History of HTN,%	14.7	12.1	11.6	10.6	11.5	7.9	6.2	5.7	6.2
History of DM, %	2.1	1.5	1.0	1.1	1.1	0.9	0.8	0.7	0.8
History of Tinnitus, %	8.4	10.5	9.3	9.5	9.4	7.6	7.9	7.7	8.1
Smoking, %									
Never	50.6	46.6	48.1	47.0	43.8	68.6	68.2	66.0	65.0
Past	24.9	29.2	28.0	29.0	30.4	19.9	20.8	22.9	24.0
Current	23.0	22.6	22.2	22.4	24.1	11.5	10.9	11.1	10.8
Alcohol, g/d	5.7 (9.3)	5.6 (9.3)	6.0 (9.4)	6.2 (9.8)	6.1 (9.9)	3.1 (6.3)	3.1 (6.1)	3.2 (6.0)	3.0 (6.0)
Physical Activity, METs/week	15.4 (27.8)	14.7 (22.9)	14.8 (19.0)	14.9 (21.1)	14.7 (21.1)	20.7 (26.8)	21.0 (27.1)	21.0 (26.8)	20.8 (26.5)
***AMED Score**	3.9 (1.7)	3.8 (1.7)	3.8 (1.7)	3.8 (1.7)	3.8 (1.7)	3.9 (1.9)	4.0 (1.9)	4.0 (1.9)	4.0 (1.9)
2+ Weeks Preterm	58.6	20.1	3.0	0.7	0.3	51.0	9.2	1.7	0.9

Abbreviations: NHS= Nurses' Health Study; lbs=pounds; BMI= body mass index; kg= kilogram; m=meter; cm= centimeter; HTN= hypertension; DM=diabetes mellitus; g= grams; METs= metabolic equivalents; AMED=alternate Mediterranean diet index; d= day

Note: Values are mean (SD) for continuous variables or % for categorical variables.

* Waist circumference was ascertained in 1986 in NHS I and 1993 in NHS II; AMED score was ascertained in 1980 in NHS I and 1991 in NHS II

Table 2:

Pregnancy-Related Characteristics of Mothers of NHS II Participants at Baseline (1992) by Birth Weight Category

	Birth Weight			
	<5.5 lbs (n=1,865)	**5.5 to <6.9 lbs (n=8,552)**	**7 to <8.5 lbs (n=14,329)**	**≥ 8.5 lbs (n=3,844)**
Maternal Characteristics				
Maternal Age at Birth (years)	26.1 (5.1)	26.0 (4.8)	26.3 (4.9)	27.0 (5.2)
Weight Gain ≥ 30 lbs During Pregnancy, %	13.1	16.1	21.5	31.9
Weight Gain <15 lbs During Pregnancy, %	27.8	17.1	11.3	7.3
Received Prenatal Care, %	97.5	98.2	98.4	98.2
Infection During Pregnancy,%	3.1	2.5	2.5	2.2
Hospitalization During Pregnancy,%	7.9	4.2	3.4	3.5
Smoking During Pregnancy,%	39.0	31.1	23.1	16.9
Preeclampsia or Eclampsia During Pregnancy,%	5.7	3.4	3.1	3.5

Abbreviations: NHS= Nurses' Health Study; lbs= pounds

Note: Values are mean (SD) for continuous variables or % for categorical variables.

Table 3:

Pooled Age-Adjusted and Multivariable-Adjusted Hazard Ratios for Risk of Moderate or Worse Hearing Loss by Birth Weight Category, Among Women in NHS I and II

	Birth Weight				
	<5.5 lbs	**5.5 to <7 lbs**	**7 to <8.5 lbs**	**≥8.5 lbs**	**P-trend**
Cases (n)	1,155	3,397	4,887	1,446	
Person-years	243,606	839,590	1,282,885	352,200	
Age-adjusted HR (95% CI)	1.14 (1.04,1.24)	1.04 (0.99,1.09)	1.00 (Ref)	1.01 (0.95,1.07)	0.02
Multivariable-adjusted HR[a] (95% CI)	1.14 (1.04,1.23)	1.05 (1.00,1.10)	1.00 (Ref)	1.00 (0.94,1.06)	0.01

Abbreviations: lbs=pounds; CI=confidence intervals; HR=hazard ratio

[a]Adjusted for age, waist circumference, physical activity, race, hypertension, diabetes, tinnitus, AMED score

Table 4:

Age-Adjusted and Multivariable-Adjusted Hazard Ratios for Risk of Moderate or Worse Hearing Loss by Gestational Age at Birth, Among Women in NHS II

	Gestational Age		
	<38 weeks	**38 to <42 weeks**	**≥42 weeks**
Cases (n)	116	673	90
Person-years	66,856	421,406	44,336
Age-adjusted HR (95% CI)	1.11 (0.91,1.37)	1.00 (Ref)	1.32 (1.05,1.66)
Multivariable-adjusted HR[a] (95% CI)	1.11 (0.90,1.35)	1.00 (Ref)	1.33 (1.06,1.65)
Multivariable-adjusted HR[b] (95% CI)	1.08 (0.87,1.34)	1.00 (Ref)	1.29 (1.03,1.62)

Abbreviations: CI=confidence intervals; HR=hazard ratio

[a]Adjusted for age, waist circumference, physical activity, race, hypertension, diabetes, tinnitus, AMED score

[b]Adjusted for covariates above, along with birth weight