Gopinath, B., Tran, Y., Tang, D., Burlutsky, G., McMahon, C., & Mitchell, P. (2022). Association between Birthweight and Hearing Loss in Older Adults. *Maturitas*. Vol.157, pp. 57-61.

which has been published in final form at:
https://doi.org/10.1016/j.maturitas.2021.11.008

Association between Birth Weight and Hearing Loss in Older Adults

Running title: Birth weight and hearing loss

Bamini Gopinath[1]

Yvonne Tran[1]

Diana Tang[1]

George Burlutsky[1]

Catherine McMahon[1]

Paul Mitchell[2]

[1]Macquarie University Hearing, Department of Linguistics, Macquarie University, NSW, Australia.

[2]Centre for Vision Research, Department of Ophthalmology and Westmead Institute for Medical Research, University of Sydney, NSW, Australia.

Correspondence to:

Bamini Gopinath

Department of Linguistics

Faculty of Medicine, Health and Human Sciences

The Australian Hearing Hub, 16 University Avenue

Macquarie University, NSW 2109, Australia

Telephone: 61-2-98508962

Email: bamini.gopinath@mq.edu.au

Abstract: 246; Text: 2443; Tables: 4

Abstract

Objectives: We aimed to examine the association between birthweight and objectively measured hearing loss in older men and women.

Study design: 893 community-dwelling participants aged 50+ years with pure-tone audiometry data and self-reported birthweight were included for cross-sectional analysis. Participants were asked how much they weighed at birth either in pounds and ounces or in kilograms and grams.

Main outcome measures: The pure-tone average of frequencies 0.5, 1.0, 2.0 and 4.0 kHz ($PTA_{0.5\text{-}4kHz}$) >25 dB HL in the better ear, established the presence of hearing loss.

Results: Around 31.9% and 50.0% of participants who self-reported low (<2.5 kg) and high birthweight (>4.5 kg), respectively, had hearing loss. The odds of experiencing any level of hearing loss (>25 dB HL) after multivariate adjustment was: OR 2.00 (95% CI 1.13-3.56) for low birthweight and OR 2.43 (95% CI 1.23-4.82) for high birthweight, compared to participants in the reference group who self-reported normal birthweight (3.1-4.0 kg). Additionally, participants with high birthweight had 2.4-fold greater odds of having mild hearing loss (25-40 dB HL). While participants with low birthweight had 2.6-fold greater odds of moderate to severe hearing loss.

Conclusions: We observed an independent U-shaped association between birthweight and age-related hearing loss, that is, persons born with low or high birthweight had a greater likelihood of experiencing any level of hearing loss in older age. These findings provide further evidence to address an important gap in the literature regarding the influence of foetal growth on the auditory system in later life.

Keywords: age-related hearing loss; birthweight; older adults; foetal growth.

1. Introduction

Age-related hearing loss is a decrease in hearing ability that occurs with age and is anticipated to be in the top 15 leading causes of the burden of disease by 2030 [1]. Age-related hearing loss is a multifactorial condition that involves several intrinsic and extrinsic risk factors such as noise exposure, smoking, and dietary factors and specific genetic risk mutations [2-7]. Moreover, it has been hypothesised that the pathogenesis underlying hearing loss in later life may originate *in utero* due to foetal growth restriction [8], typically indicated by low birthweight for gestational age. Among low-birth-weight infants, exposure to stress or undernutrition *in utero* could result in adverse alterations to the cochlear microcirculation; as cochlear reserve declines with aging, these changes may lead to hearing loss later in life [9].

While low birth weight is associated with a higher risk of neonatal hearing loss [10], there is a dearth of population-based studies that have examined the association between birth weight and hearing loss in older adults. *Barrenäs et al.* [11] showed that in Swedish men aged 17-24 years, low birth weight for gestational age was associated with a slightly increased risk of a hearing loss at high frequencies. More recently, *Gupta et al.* [9] showed that in women, 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 of hearing loss. However, both these studies assessed associations between birth weight and hearing loss in either men or women only, limiting the generalisability of these study findings and furthermore, the study by *Gupta et al.* [9] only examined self-reported hearing loss. Our study aimed to move the research forward in this area by addressing some of the limitations of these previous studies, namely, by assessing the independent associations between birthweight (in kg) and objectively measured hearing loss (any, mild or moderate to severe hearing loss) in both community-dwelling men and women aged 50+ years.

2. Methods

2.1 Study population

The Blue Mountains Hearing Study (BMHS) was a population-based survey of age-related hearing loss conducted during 1997-2007 among participants of the Blue Mountains Eye Study (BMES) cohort [12]. During 1992-4, 3,654 participants aged 50 years or older were examined (82.4% participation; BMES-1). Surviving baseline participants were invited to attend 5-year follow-up examinations (1997-9, BMES-2), at which 2334 (75.1% of survivors) and an additional 1174 newly eligible residents were examined, i.e. those who had moved into the study area or study age group (Extension Study. Hearing was measured at BMES-2 (i.e. 1997-99) i.e. 2956 participants aged ≥50 y had audiometric testing performed at BMES-2 (i.e. BMHS). The study was approved by the Human Research Ethics Committee of the University of Sydney and was conducted adhering to the tenets of the Helsinki Declaration. Signed informed consent was obtained from all the participants at each examination.

2.2 Audiological examination

Pure-tone audiometry at both visits was performed by audiologists in sound-treated booths, using standard TDH-39 earphones and Madsen OB822 audiometers (Madsen Electronics, Copenhagen, Denmark), calibrated regularly to Australian standards. Audiometric thresholds for air-conduction stimuli in both ears were established for frequencies at 250, 500, 1000, 2000, 4000, 6000 and 8000 Hz. We determined hearing impairment as the pure-tone average of audiometric hearing thresholds at 500,1000, 2000, and 4000 Hz ($PTA_{0.5\text{-}4kHz}$), defining any level of hearing loss as $PTA_{0.5\text{-}4kHz}$ >25 dB hearing level (HL), in the better of the two ears. This defined hearing loss as bilateral. Bone conduction was also evaluated whenever air conduction thresholds were greater than 15-dB hearing level (dB HL) at 4 frequencies (500, 1000, 2000, and 4000 Hz). Participants were examined for any evidence of collapsed canals, and if present, air conduction thresholds at the higher frequencies were reassessed, taking care to reduce pressure on the external ear. The audiologist also performed otoscopic evaluation and examined the ears for wax occlusion, and if present, the participants were asked to return for assessment after treatment [13].

2.3 Assessment of study factor (birth weight) and potential covariates

A comprehensive medical history that included information about hearing, demographic factors, socio-economic characteristics and lifestyle factors, was obtained from study participants. The medical history included presence of cardiovascular or other systemic disease and associated risk factors, medications used, exercise, smoking, and consumption of caffeine and alcohol. Participants were asked how much they weighed at birth either in pounces and ounces or in kilograms and grams. For the purposes of this study, if participants reported their birthweight in pounds and ounces we converted this to SI (System International) units. Several validation studies have previously demonstrated the reliability of self-report of birth weight and preterm birth [14, 15]. Based on our previous publication analysing birth weight in the Atherosclerosis Risk in Communities (ARIC) study [16], we categorized the remaining participants into 5 ordered birthweight categories (<2.5 kg, 2.5 to 3.0 kg, 3.1 to 3.5 kg, 3.6 to 4.0 kg, and 4.1 to 4.5 kg). The reference group was 3.1-4.0 kg in line with the reference group reported in the study by *Gupta et al*. [9].

An audiologist also asked questions around history of any self-perceived hearing problem, including its severity, onset and duration, whether help was sought for this from primary care practitioners or other professionals, and if a hearing aid was provided. Additional questions included family history of hearing loss, past medical and/or surgical treatment of otologic conditions, other diseases associated with hearing loss, and risk factors for impaired hearing such as body mass index, hypertension and diabetes. Exposure to noise at work, or during military service or leisure activities was also determined.

2.4 Statistical analysis

SAS statistical software (SAS Institute, Cary NC) version 9.4 was used for analysis including χ^2-tests, ANOVA and logistic regression. Data around study characteristics of participants was summarised using either F-test (One-way ANOVA) for continuous variables (expressed as means and standard deviation) or PROC FREQ for categorical variables (expressed as n, %). The association between birth weight and hearing loss was examined in logistic regression models, adjusting first for age and sex. We then further adjusted for confounders previously found to be significantly associated with birthweight and/or hearing loss prevalence (family history of hearing loss, smoking, workplace noise exposure, body mass index, and previous history of diabetes and hypertension) [2, 6, 13]. However, only smoking, family history of hearing loss and prior workplace noise exposure remained as significant covariates in the multivariate model and were therefore, included in the final parsimonious model. Results of all cross-sectional analyses are expressed as adjusted odds ratios (OR) with 95% confidence intervals (CI). *P*-values <0.05 indicated statistical significance.

3. Results

Among participants with complete audiological data at baseline (n=2015), 68 participants were excluded on the basis that they had conductive hearing loss, middle ear hearing loss, childhood hearing loss and/or a history of diagnosed otosclerosis. An additional 15 participants were excluded as they reported previous head injury. Of the remaining, a total of 893 subjects also reported their birth weight and so, were included in the final analysis. Table 1 shows that participants who reported low birthweight for gestational age (<2.5 kg) versus participants in the other birthweight categories were more likely to be younger, male and have hypertension but less likely to be a current smoker. Figure 1 shows the prevalence of hearing loss by birthweight in our cohort. Just under one in three participants who reported low birthweight (<2.5 kg) had any level of hearing loss (>25 dB HL) compared to just under one in four participants with normal birthweight (3.1-4.0 kg). While around one in two participants who were high birth weight for gestational age (>4.5 kg) had any level of hearing loss at age 50+ years (Figure 1).

Compared to participants in the reference group (i.e. normal birth weight of 3.1-4.0 kg), those who reported low (<2.5 kg) or high birth weight (>4.5 kg) for gestational age, had greater odds of any level of hearing loss (>25 dB HL) after adjusting for age, sex, smoking status, family history of hearing loss and workplace noise exposure: OR 2.00 (95% CI 1.13-3.56) and OR 2.43 (95% CI 1.23-4.82), respectively (Table 2). Table 3 shows that after multivariate adjustment, participants with high birth weight (>4.5 kg) had 2.4 greater odds of having mild hearing loss (25-40 dB HL). While participants with low birth weight (<2.5 kg) had 2.6 greater odds of developing moderate to severe hearing loss in later age (Table 4).

4. Discussion

Despite a link between low birthweight and higher risk of childhood hearing loss being established [10], few population-based studies of adults have assessed whether birthweight influences the decline in hearing in later life. In our study, we observed an independent U-shaped association between birthweight and age-related hearing loss in adults aged 50+ years. Just under one in three participants aged 50+ years who self-reported low birthweight for gestational age (<2.5 kg), had any level of measured hearing loss. While around half of participants who reported high birthweight (>4.5 kg) had age-related hearing loss. Compared to participants with normal birthweight (3.1-4.5 kg), those who self-reported low and high birthweight for gestational age had ~2.0- and 2.4-fold greater likelihood of experiencing bilateral hearing loss in later life, respectively, after multivariate adjustment. These epidemiological data provide further support for the independent influence of birth weight - a marker of the intrauterine environment, on the auditory system that may involve subclinical pathologic changes which are not apparent until later in adulthood [9].

In our study, low birth weight defined as <2.5 kg was independently associated with any level of hearing loss (>25 dB HL) and moderate to severe hearing loss (40-60 dB HL). These findings concur with prior studies showing that among low-birth-weight infants, the prevalence of sensorineural hearing loss is higher than in the general new-born population, and this is hypothesised to be due to complications of low birth weight such as hypoxia and hyperbilirubinemia [9, 17, 18]. Similarly, our observed associations concur with findings from a US cohort of women [9] and a Swedish cohort of young men [11]. For instance, *Gupta et al.* [9] recently reported a modestly higher risk of adult-onset moderate or greater hearing loss among those participants with low birth weight. These findings together have important clinical implications for closer monitoring and screening of these individuals for hearing loss beyond childhood; and indicates that foetal growth restriction reflected by a reduced birth size might need to be considered as a potential risk factor for age-related hearing loss.

Namely, our findings support the view that the ‘thrifty phenotype hypothesis’ or ‘foetal programming’ could be a plausible explanation for the development of hearing loss; and suggests that hearing loss in later life could have the same underlying causes as growth retardation *in utero* [11]. According to this hypothesis, events during foetal life, such as alterations to foetal blood flow or hormone levels as a result of e.g., stress or malnutrition, could lead to abnormal development of the organ systems involved in blood pressure regulation and glucose control [19-21]. These adaptations during foetal life may become permanently programmed, persisting throughout life and leading to chronic diseases in adulthood. For example, cardiovascular disease, hypertension, diabetes and hypercholesterolaemia are linked to reduced foetal growth and hence, low birth weight [19, 22, 23]. These chronic health conditions were all identified as risk factors for hearing loss in previous studies of adults [24-26]. It is possible that similar mechanisms may underlie the development of age-related hearing loss [9].

Moreover, it is posited disruptions to the vasculature *in utero* could lead to disturbances in the cochlear microcirculation and endothelial dysfunction, thereby, predisposing an individual to age-related hearing loss due to reduced cochlear reserve [9]. For instance, we previously showed that persons born with lower birthweight have narrower retinal arterioles [16], a structural microvascular marker of hypertension and related cardiovascular disease, as well as being linked to age-related hearing loss [27]. With the ageing process, degeneration of cochlear synapses and loss of hair cells may diminish cochlear reserve, increasing the predisposition to develop hearing loss in later life [9, 28]. On the other hand, there could be early changes to gene expression impacting on auditory function in older age [4]. Therefore, it is plausible that the higher risk of age-related hearing loss observed in our study, is likely due to a combination of pre- and/or postnatal factors such as microvascular disease, ageing, genetic and hormonal factors [9].

During the last two decades, interest in the potential health risks associated with high birthweight has also emerged, and associations between high birthweight and the risk of adverse health outcomes (e.g. overweight/ obesity, diabetes, and cardiovascular disease) have been studied in an increasing number of studies [29]. We show for the first time that participants who reported high birthweight (>4.5 kg) had a greater likelihood of any or mild hearing loss at age 50+ years. The link between high birthweight and age-related hearing loss could be mediated through the same pathophysiological mechanisms that underlie the development of chronic diseases such as diabetes and cardiovascular disease, as both conditions are posited to have a role in the development of hearing loss in later life. Given that this association between high birthweight and age-related hearing loss is a novel finding, further large population-based cohort studies are needed to verify our observed association.

Key strengths of our study include its representative, population-based sample of older men and women. Further, we used standardised, audiometric testing to measure hearing sensitivity. There are, however, study limitations that deserve further mention. Firstly, we used self-reported birthweight rather than data collected through birthweight records. Nevertheless, this was previously shown to have moderate to high correlation with actual birthweight (0.8642) and is often the only practical means of recording birthweight information in large epidemiological studies [16]. Self-reported birthweight is also reported to underestimate, rather than bias, associations between birth weight and adult outcomes [30]. Secondly, only ~46% of our sample reported birthweight and were included in the analyses and this could have introduced selection bias. Finally, because these data are cross-sectional, our study cannot definitively establish cause and effect. However, the most likely direction of the association is that birthweight is related to greater likelihood of age-related hearing loss as the reverse direction of effect (hearing loss leading to low/ high birthweight) is unlikely.

In summary, our study demonstrates a novel U-shaped association between birthweight and age-related hearing loss, with both low and high birthweight independently associated with ~2-fold greater odds of developing hearing loss in older age. Therefore, these epidemiological data suggest that birthweight (a marker of intrauterine growth) impacts on the development of the inner ear and therefore, influences the risk of developing hearing loss. Our findings provide further evidence to address an important gap in the literature regarding the influence of foetal growth on the auditory system; and could have clinical implications for screening and management of hearing loss throughout the life course for individuals who were low or high birthweight for gestational age.

Sources of support

The Blue Mountains Eye and Hearing Studies were supported by the Australian National Health and Medical Research Council (Grant Nos. 974159, 991407, 211069, 262120). The funders had no role in the conduct of the research or preparation of this manuscript.

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Figure 1. Prevalence of hearing loss by birthweight categories in the Blue Mountains Hearing Study

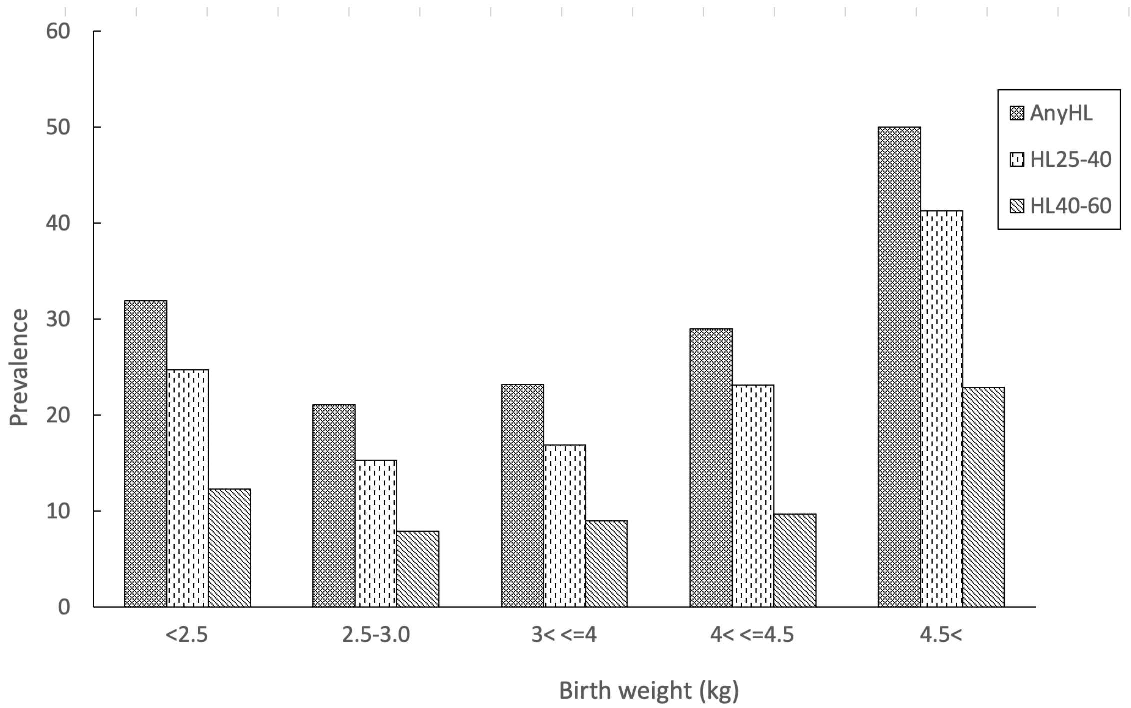

Table 1. Study characteristics of Blue Mountains Hearing Study participants (n=893) stratified by birthweight categories.

	Birthweight, kg					
Characteristics	**<2.5 (n=97)**	**2.5-3.0 (n=147)**	**3.1-4.0 (n=411)**	**4.1-4.5 (n=184)**	**>4.5 (n=54)**	***P***
Age, yrs	64.4 (8.3)	64.6 (8.3)	64.5 (8.7)	66.4 (8.8)	69.3 (7.9)	**0.001**
Male sex	23 (23.7)	41 (27.9)	154 (37.5)	81 (44.0)	32 (59.3)	**<0.0001**
Body Mass Index, kg/m^2	28.3 (5.8)	26.9 (4.6)	28.1 (5.1)	28.5 (4.6)	28.6 (5.7)	0.09
Current smoker	8 (8.4)	16 (11.1)	40 (9.8)	14 (7.6)	6 (11.3)	**0.002**
Family history of hearing loss	43 (45.7)	75 (51.0)	207 (50.5)	77 (42.1)	20 (37.0)	0.14
Exposure to workplace noise	28 (29.8)	50 (34.3)	137 (33.5)	75 (41.4)	22 (41.5)	0.22
Type 2 diabetes	9 (9.3)	14 (9.5)	34 (8.3)	11 (6.0)	6 (11.1)	0.68
Hypertension	61 (62.9)	67 (45.6)	193 (47.0)	105 (57.1)	27 (51.9)	**0.01**

*Data are presented as n (%) or mean (SD), unless otherwise stated

Table 2. Association between birthweight and any hearing loss (>25 dB HL) presented as adjusted odds ratios (OR) and 95% confidence intervals (CI)

Birth weight (kg)	Any level of hearing loss, OR (95% CI)	
	Age-sex adjusted	**Multivariable adjusted***
<2.5 (n=94)	**2.08 (1.18-3.65)**	**2.00 (1.13-3.56)**
2.5-3.0 (n=147)	0.94 (0.56-1.58)	0.95 (0.56-1.62)
3.1-4.0 (n=410)	1.00 (reference)	1.00 (reference)
4.1-4.5 (n=183)	1.06 (0.68-1.66)	1.06 (0.67-1.68)
>4.5 (n=54)	**2.02 (1.05-3.90)**	**2.43 (1.23-4.82)**

*Further adjusted for smoking status, family history of hearing loss and exposure to workplace noise.

Table 3. Association between birthweight and mild hearing loss (25-40 dB HL) presented as adjusted odds ratios (OR) and 95% confidence intervals (CI)

	Mild hearing loss, OR (95% CI)	
Birth weight (kg)	**Age-sex adjusted**	**Multivariable adjusted***
<2.5 (n=85)	**1.95 (1.05-3.63)**	1.85 (0.98-3.50)
2.5-3.0 (n=137)	0.94 (0.53-1.67)	0.93 (0.51-1.69)
3.1-4.0 (n=379)	1.00 (reference)	1.00 (reference)
4.1-4.5 (n=169)	1.08 (0.66-1.78)	1.06 (0.64-1.76)
>4.5 (n=46)	**2.10 (1.03-4.26)**	**2.41 (1.16-5.04)**

*Further adjusted for smoking status, family history of hearing loss and exposure to workplace noise.

Table 4. Association between birthweight and moderate to severe hearing loss (>40 dB HL) presented as adjusted odds ratios (OR) and 95% confidence intervals (CI)

	Moderate to severe hearing loss, OR (95% CI)	
Birth weight (kg)	**Age-sex adjusted**	**Multivariable adjusted***
<2.5 (n=73)	**2.51 (1.01-6.25)**	**2.56 (1.02-6.44)**
2.5-3.0 (n=126)	1.07 (0.46-2.47)	1.10 (0.45-2.66)
3.1-4.0 (n=346)	1.00 (reference)	1.00 (reference)
4.1-4.5 (n=144)	0.95 (0.45-2.02)	1.04 (0.47-2.27)
>4.5 (n=35)	1.71 (0.62-4.71)	2.41 (0.83-7.06)

*Further adjusted for smoking status, family history of hearing loss and exposure to workplace noise.