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Early Life Influences on Hearing in Adulthood: a Systematic Review and Two-Step Individual Patient Data Meta-Analysis

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Objectives: Adverse prenatal and early childhood development may increase susceptibility of hearing loss in adulthood. The objective was to assess whether indices of early development are associated with adult-onset hearing loss in adults ≥18 years.

Design: In a systematic review and meta-analysis, four electronic databases were searched for studies reporting associations between indices of early development (birth weight and adult height) and adult-onset hearing loss in adults ≥18 years. We screened studies, extracted data, and assessed risk of bias. Authors were contacted to provide adjusted odds ratios from a logistic regression model for relationships between birth weight/adult height and normal/impaired hearing enabling a two-step individual patient data random-effects meta-analysis to be carried out. The study is registered with PROSPERO, CRD42020152214.

Results: Four studies of birth weight and seven of adult height were identified. Three studies reported smaller birth weight associated with poorer adult hearing. Six studies reported shorter height associated with poorer hearing. Risk of bias was low to moderate. Four studies provided data for two-step individual patient data random-effects meta-analysis. Odds of hearing impairment were 13.5% lower for every 1 kg increase in birth weight [OR: 0.865 (95% confidence interval: 0.824 to 0.909)] in adulthood over two studies (N=81,289). Every 1 cm increase in height was associated with a 3% reduction in the odds of hearing impairment [OR: 0.970 (95% confidence interval: 0.968 to 0.971)] over four studies (N=156,740).

Conclusions: Emerging evidence suggests that adverse early development increases the likelihood of hearing impairment in adulthood. Research and public health attention should focus on the potential for prevention of hearing impairment by optimizing development in early life.

Key words: Birth weight, Developmental hypothesis of disease, Fetal origins, Hearing.

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INTRODUCTION

The 2019 Global Burden of Disease study (Haile et al. 2021) identified hearing loss as the third leading cause of years lived with disability. As hearing loss has become a major public health concern, reducing the global burden of hearing loss has become an international priority (Wilson et al. 2017). A growing body of evidence indicates that early developmental factors seem to have a major influence on adult hearing function. Addressing early developmental factors may therefore offer an opportunity to prevent hearing loss and reduce the associated global burden of disease (Barrenäs et al. 2003; Nafstad et al. 2002; Olsen et al. 2001).

According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, several noncommunicable diseases including type 2 diabetes, hypertension, and coronary heart disease have their origins in early life (Barker et al. 2002; Barker et al. 2005; Eriksson et al. 1999; Hales et al. 1991; Hanson & Gluckman 2014; von Bonsdorff et al. 2011). It is believed that especially during the first 1000 days of life (including pregnancy) there are important hormonal, nutritional, and metabolic factors that influence and program later health in adulthood. The DOHaD hypothesis has its origins in work by David Barker and colleagues who observed that the geographical areas in the United Kingdom that had the highest infant mortality rates in the 1920s also had the highest rates of heart disease in the 1970s (Barker & Osmond 1986). Because the most reported cause of infant mortality was low birthweight, Barker suggested that poor nutrition in early life may increase susceptibility to disease in later life. Barker et al. (1993) and Barker et al. (1989) subsequently examined associations between birthweight, ponderal index, head circumference, and heart disease in later life among men born in the early 20th century in two United Kingdom counties and reported that reduced fetal growth was followed by increased mortality from heart disease in adulthood. People who were born small for gestational age were at risk, rather than those born prematurely. Similar associations were subsequently reported in women [e.g., Rich-Edwards et al. (1997)] and in numerous other studies in other countries [e.g., Stein et al. (1996)]. The most straight forward explanation for the association between low

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birthweight and heart disease in adulthood might be that both are caused by shared environmental factors. However, correction for risk factors for heart disease in adulthood including smoking, diet, and exercise does not attenuate associations between birth weight and risk of heart disease in adulthood [e.g., Leon et al. (1998); Rich-Edwards et al. (1997)].

Traditional markers of non-optimal growth during fetal life in the DOHaD-field are birth weight and birth length (Kline et al. 1989), while height has been used as a marker of nutritional conditions during childhood (Wadsworth et al. 2002). Investigation of the DOHaD hypothesis in humans primarily involves large-scale epidemiological modelling of associations between early life exposures (indexed by birth weight or height) and outcomes in adulthood, accounting for potential confounds including sex and ethnic background. Ethical considerations preclude experimental study of the DOHaD hypothesis in humans [although there are horrifying natural experiments, such as the Dutch Hunger Winter of 1944 to 1945 (Poupakis et al. 2019)].

As an example of epidemiological research on the DOHaD hypothesis, Rich-Edwards and colleagues (1997) examined associations between birth weight and cardiovascular disease in adulthood in a cohort of 121,700 American women in the longitudinal Nurses' health study. Health outcomes were surveyed every two years via questionnaire. The main outcome was nonfatal cardiovascular disease, including myocardial infarction, coronary revascularisation, and stroke. Among 70,297 women who reported being free of cardiovascular disease in the baseline 1992 questionnaire, there were 1216 cases of subsequent nonfatal cardiovascular disease. The lowest quintile of birth weight (<2268 g) had a relative risk of 1.49 (95% confidence interval: 1.05 to 2.10) compared with the highest quintile, with a statistically significant trend for increasing risk for nonfatal cardiovascular disease with lower birth weight quintile. The analysis was restricted to women who were singleton births and had been born at full term. Analysis statistically controlled for potential confounders including socioeconomic group and lifestyle factors (alcohol consumption, saturated fat intake, and physical activity). The authors concluded that the results provide strong evidence of association between birth weight and cardiovascular disease in adulthood.

Smaller size and birth has subsequently been linked to other risks for heart disease, including diabetes, high blood pressure and hyperlipidaemia (Forsen et al. 2000; Hales & Barker 1992; Hales et al. 1991; Huxley et al. 2000) and other noncommunicable diseases in adulthood (Barker 2004). Research further suggests an impact of early life factors on cognitive functioning (Grove et al. 2017), visual acuity (Olsen et al. 2001), and hearing (Barrenäs et al. 2003) in adulthood.

There is experimental evidence supporting the DOHaD hypothesis from animal models [e.g., Morrison et al. (2018)], including evidence for effects on cognitive and sensory outcomes (Rice & Barone 2000). Possible mechanisms for early developmental effects on adult hearing function include undernutrition limiting development of the brain and sensory organs (Barker 2004), modulation of HPA-axis (hypothalamus-pituitary-adrenal), growth factors affecting neurosensory development (Barrenäs et al. 2003; Camarero et al. 2001; Canlon et al. 2003; Seckl 2004), or alterations in gene expression that affect hearing (Egger et al. 2004; Provenzano & Domann 2007). Alternatively, early developmental factors may increase susceptibility to diabetes and cardiovascular disease (Barker 2004), and hearing loss has been linked to cardiovascular disease and diabetes (Helzner et al. 2011; Horikawa et al. 2013).

Early developmental factors program a metabolic/health/growth trajectory over the lifespan, which interacts with age-related declines in physiological plasticity and accumulated challenges to health to increase susceptibility to noncommunicable disease (Hanson & Gluckman 2011). The implication of such a life course model of disease is that the effectiveness of health interventions in adulthood is limited. Early intervention during developmentally more plastic periods has a much greater impact in altering adverse trajectories and preventing disease. Early developmental factors may have small effects, but because of universal exposure, developmental factors are major determinants of prevalence of disease at a population level (Rice & Barone 2000). Early developmental factors have been recognized as research priorities in relation to heart disease, diabetes, and dementia (European Parliament 2011; Hendrie et al. 2006). Early developmental factors warrant similar attention in relation to reducing the burden of hearing impairment.

No systematic review has examined the relationship between early developmental factors and adult hearing. We conducted a systematic review and meta-analysis of studies that modelled the relationship between early developmental indices birth weight and adult height and hearing in adult populations. We aimed to assess whether early developmental indices are associated with adult hearing loss and to quantify the strength of these associations.

MATERIALS AND METHODS

The protocol for this review was listed with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42020152214. Acquisition, extraction, assessment, and reporting of data was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (Moher et al. 2009).

Eligibility Criteria

Studies were eligible for inclusion if they included adult participants over 18 years of age and reported hearing data in relation to birth weight and/or adult height. All observational study types were included. Studies were excluded if they focused on low birth weight populations (<2.5 kg) or were not peer reviewed reports. There were no restrictions on publication date or language of publication. The data sources below include publications in languages other than English. If the search identified articles in other languages, the authors had access to professional translation via the Department of Linguistics at Macquarie University. Given the range of hearing measures used, we took an inclusive approach to the hearing outcome measures of interest. The inclusion criteria were (1) studies reported focusing on acquired adult-onset hearing loss, (2) hearing impairment identified on the basis of pure tone audiometric testing (e.g., audiometric threshold over >40 dB HL), or self-reported hearing problems, or registration for hearing impairment in state or private patient databases, or speech in noise performance (e.g., speech recognition threshold >−5.5 dB signal-to-noise ratio). Audiometric, speech recognition in noise, and self-report indexes of hearing correlate strongly with each other (r's ~ 0.7) (Nondahl et al. 1998; Smits et al. 2004).

The Australian Blue Mountains hearing study estimated high sensitivity, specificity, positive predictive value and negative predictive value rates of 78%, 67%, 61%, and 82% of self-report hearing measures against audiometrically identified hearing impairment (Sindhusake et al. 2001); the American Epidemiology of Hearing loss study (Nondahl et al. 1998) reported similar rates (71%, 71%, 68%, and 74%). With respect to speech recognition in noise, Koole and colleagues (2016) investigated the Digits in Noise Test in relation to identification of audiometric hearing loss. They reported a strong correlation of 0.8 between the Digits in Noise and audiometric threshold. Analysis of receiver operating characteristics yielded an area under the curve of 0.98 with respect to detection of moderate hearing loss.

Data Sources

The search strategy included searches of electronic databases and hand-searching the reference lists of eligible papers for additional studies. The electronic database search included MEDLINE, Embase, PsychINFO, and CINAHL. Search terms were (height OR stature OR birth weight OR birth size OR fetal growth OR prenatal nutrition OR fetal development OR growth in utero OR intrauterine growth OR fetal growth retardation) AND (hearing OR deaf*). The search was carried out in March 2021 with no restriction on date of publication.

Study Selection

P.D. and J.N. independently reviewed all the potential studies against the inclusion criteria. The study abstracts and full-text manuscripts were chosen for further review if the title related to evaluation of adult hearing function in relation to birth weight and/or adult height. Any uncertainty over inclusion was discussed among the coauthors. The study selection process and reasons for exclusion were recorded (Fig. 1).

Data Extraction and Analysis

A data extraction form was created and adapted following piloting as appropriate for the present review. Data were extracted from the full-text article by PD and reviewed by a second author (J.N.). Disagreements resolved via discussion with an additional reviewer.

A two-step individual patient data meta-analysis was planned in which the first step involved inviting article authors to provide the log odds ratio and standard error from a logistic regression for the relationships between birth weight/adult height and adult hearing status after adjusting for age at testing, gestational age, sex, and socioeconomic status at birth and combinations of these predictors (if possible). Following previously observed nonlinear relationships between birth weight and adult hearing (Dawes et al. 2015) and in order to focus on variation within the normal range, the analysis of associations between birth weight and adult hearing were restricted to birth weights between 2.5 and 4.5 kg for all included studies. The developmental hypothesis focuses on variation within the *normal range* of birth weights, excluding very low birth weight or premature babies as well as those that are large for gestational age ("fetal macrosomia"). A range of outcomes (including hearing) are known to be poorer for low birth weight and large for gestational age babies, and the mechanisms are thought to be distinct from those hypothesized for the developmental hypothesis of disease (Hack et al. 1995; Xu et al. 2010).

In the second step, the estimated effect (log odds ratio and standard error) of birth weight/adult height on hearing impairment from each study was pooled using a random-effects model with the Paule-Mandel estimator for between studies variability. Results were exponentiated to provide odds ratios with 95% confidence intervals. Individual patient data meta-analysis is equivalent to a reanalysis of all available raw data while controlling for within and between-study variability, thus providing stronger results than a standard meta-analysis. Where article authors were not able to provide the summaries required, these studies were included in a narrative review. Heterogeneity was assessed using p-values from Cochran's Q statistic and I^2, the proportion of variability between studies due to heterogeneity. Publication bias was planned to be evaluated by funnel plot analysis if at least 10 studies were included in the meta-analysis.

Risk of bias was independently assessed with the Quality in Prognostic Studies (QUIPS) tool (Hayden et al. 2013) by two authors (P.D. and J.N.). The QUIPS was informed by epidemiologic principals and developed following systematic review of quality assessment in prognostic studies by a working group of epidemiologists, statisticians, and clinicians. The QUIPS tool supports systematic appraisal of bias in studies of prognostic factors related to participation, attrition, prognostic factor measurement, confounding measurement, and analysis and reporting. The QUIPS tool is widely used in systematic reviews (on diverse topics, such as dementia prevention and care (Livingston et al. 2020), chronic pain (Mansfield et al. 2016) and early childhood caries (Tinanoff et al. 2019); Hayden et al. (2013) had 1437 citations in Google scholar as of July 2021). The QUIPS has moderate to substantial inter-rater reliability (Hayden et al. 2013). Disagreements in QUIPS ratings were resolved via discussion.

RESULTS

Four studies were identified that reported on birth weight (Table 1), with seven studies reporting associations with adult height and hearing in adulthood (Table 2). Risk of bias ratings were low to moderate according to QUIPS criteria (Appendix 1 in Supplemental Digital Content 1, http://links.lww.com/EANDH/A972) and suggested a generally low level of bias. The most common failing was incomplete reporting of participant attrition (e.g., response rates, descriptions of attempts to collect information on participants who dropped out or did not consent to participate, reasons for participants being lost to follow-up being reported, reporting of outcome and prognostic factor information on those who dropped out or did not participate). Publication bias was not assessed as the required minimum number of studies for bias analysis was not met.

All studies were either conducted in Sweden, Denmark, or the United Kingdom. Several studies reported analysis of data from samples of young males conscripted for military service (Axelsson et al. 1994; Barrenäs et al. 2005a,b; Olsen et al. 2001). The remaining samples indexed adult hearing in populations that included men and women aged over 18 (Olsen et al. 2001), middle-aged (Dawes et al. 2015) or older people (Batty et al. 2017; Sayer et al. 1998). Birth weight was either based on self-report or extracted from birth records. Self-reported birth weight is a reliable (r's > 0.8) index of birth weight (Sanderson et al. 1998) that is routinely used in DOHaD studies (e.g., Lawlet-Heavner et al. 1994; Tyrrell et al. 2013). Hearing was indexed

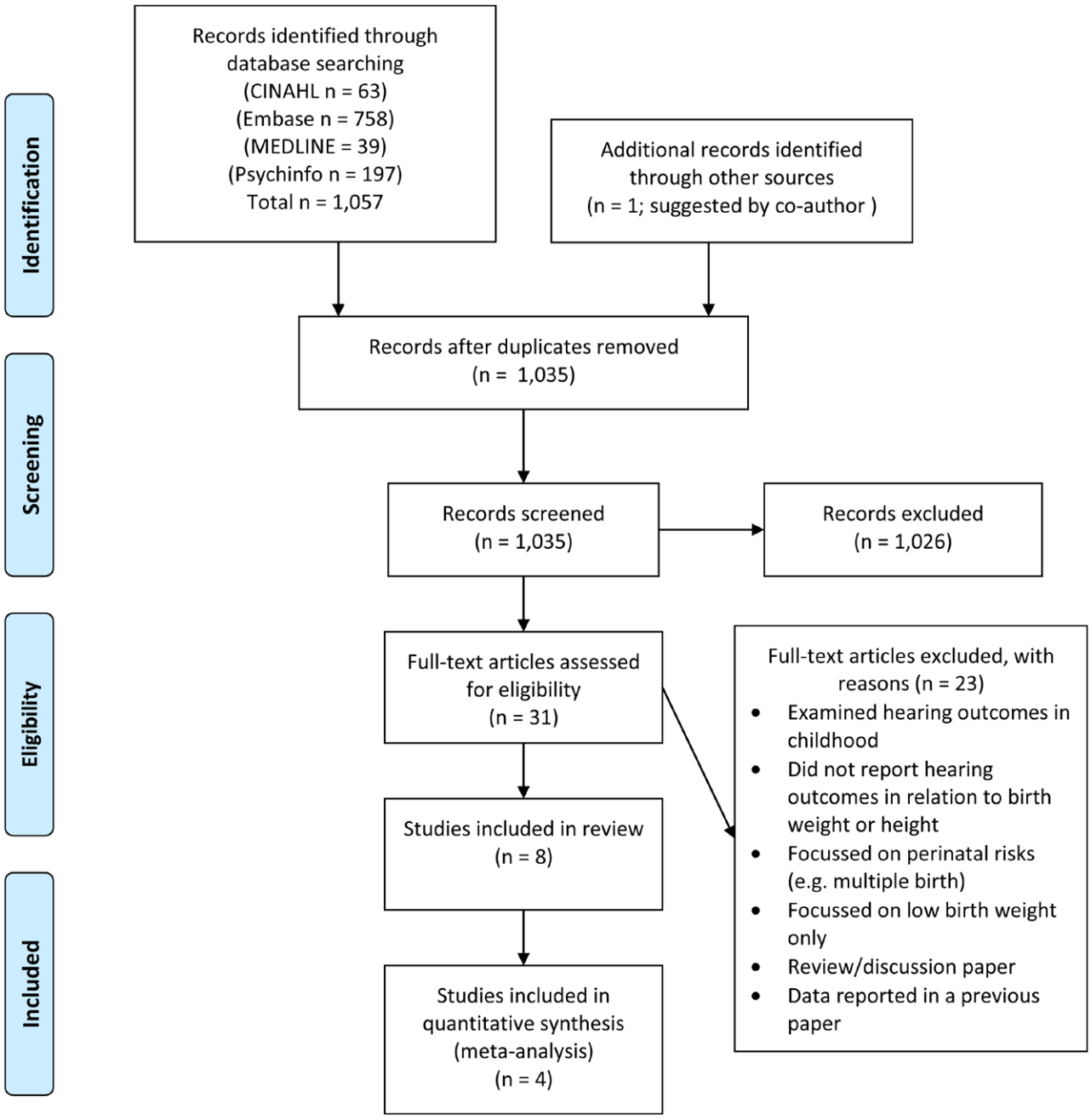

Fig. 1. Flow diagram to illustrate the study selection process.

by self-reported hearing problems, pure tone audiometric assessment, or speech recognition in noise testing.

Provision of logistic modelling summaries after adjusting for the required predictors (Appendix 2 in Supplemental Digital Content 1, http://links.lww.com/EANDH/A973) enabled two-step individual patient data meta-analysis combining two studies for birth weight and four studies for height. Required data were not available for the remaining studies due to data being deleted in accordance with data retention policy, data no longer being in a format that was readable or data not being found. The first step of the two-step individual patient data meta-analysis was conducted only adjusting for age at testing and sex; data were not available for adjustment for gestational age and/or socioeconomic status at birth for all studies (Appendix 2 in Supplemental Digital Content 1, http://links.lww.com/EANDH/A973).

Birth Weight

Three out of four studies reported associations between birth weight and adult hearing, with smaller birth weight associated with poorer hearing in adulthood (Table 1). The three studies that reported an association (Barrenäs et al. 2005b; Dawes et al. 2015; Olsen et al. 2001) had substantially larger sample sizes than the study that did not report an association (Sayer et al. 1998). Only two studies controlled for gestational age (Barrenäs et al. 2005b; Olsen et al. 2001). Two studies reported that only

TABLE 1. Studies reporting associations between birth weight and adult hearing

First Author, Publication Year	Population; Setting	Sample Size, Sex, and Age	Exclusion Criteria	Study Design	Early Life Exposures	Hearing Outcome	Results
Barrenäs et al. (2005b)	Army conscripts, Sweden	N=245,092; 100% male; aged around 18 yrs. Mean ages and distributions not reported.	Multiple birth, non-Nordic background	Longitudinal follow-up of a birth cohort	Birth weight, birth length, head circumference (<–2SD, –2 to +2 SD, or >2SD)	Pure tone audiometric hearing impairment (>20 dB HL at 2, 4 and 6 kHz (mid frequency) and 1 and 2 kHz (high frequency) in the poorer ear).	Birth weight <–2 SD associated with increased odds of poor high frequency hearing (1.20; 1.13–1.49) (versus –2 to 2 SD range). Adjusted for birth length, head circumference, gestational age, height and BMI.
Dawes et al. (2015)	Adults, United Kingdom	Birth weight analysis: n=80,572; 42.0% male; aged 40–69 yrs	None reported	Cross sectional	Self-reported birth weight	Speech-in-noise recognition threshold (signal-to-noise ratio) in the better ear.	Birth weight associated with hearing (β 0.01, $p<0.01$). No association with 4 yr change in hearing. Adjusted for sex, age, social economic status, education level, smoking, cardiovascular disease, diabetes, hypertension, cholesterol, maternal smoking.
Olsen et al. (2001)	Army conscripts, Denmark	N=4300; 100% male; aged around 18 yrs. Mean ages and distributions not reported	Conscripts wearing contact lenses Born outside Denmark, or before 1 January 1973	Longitudinal follow-up of a birth cohort	Birth weight	Pure tone audiometric hearing impairment (>40 dB HL over 500–2000 Hz).	Only low birth weight (<2500 gm) was associated with hearing impairment (1.62; 1.0–2.6). Adjusted for gestational age, mothers age, parity, occupational status and marital status.
Sayer et al. (1998)	Adults born in Hertfordshire between 1920 and 1930, United Kingdom	N=717 (57% male); average age 67.5 yrs	None reported	Longitudinal follow-up of a birth cohort	Birth weight and weight at 1 yr	Pure tone audiometric threshold (frequency range not reported)	No association with birth weight and hearing. Decreasing weight at 1 yr associated with poorer hearing threshold. Only *p*-values reported. Adjusted for age, sex, social class and adult height

BMI, body mass index.

low birth weight [<2.5 kg; Olsen et al. (2001); <−2 SD; Barrenäs et al. (2005b)] was associated with adult hearing.

In the two-step individual patient data meta-analysis, pooling summaries from two studies (Dawes et al. 2015; Sayer et al. 1998), n=81,615, normal range birth weight (2.5 to 4.5 kg) was significantly associated with higher odds of normal hearing after adjusting for age at testing and sex ($p < 0.0001$), with a 13.5% decrease in likelihood of hearing loss for each 1 kg increase in birth weight (Fig. 2, top). There was no significant heterogeneity between studies ($I^2 = 0$, $p = 0.85$).

Adult Height

All seven studies reported that shorter stature was significantly associated with poorer hearing (Table 2). Studies typically adjusted for age, sex, current social economic position and/or educational level, noise exposure, health conditions, and health behaviours (including smoking and physical activity). Studies did not adjust for socioeconomic position at birth. The two studies that analyzed changes in hearing longitudinally reported no association with height (Burr et al. 2005; Dawes et al. 2015).

Two-step individual patient data meta-analysis pooling data from four studies (Batty et al. 2017; Burr et al. 2005; Dawes et al. 2015; Sayer et al. 1998), n = 165,890, found that hearing status was significantly associated with adult height after adjusting for age at testing and sex ($p < 0.0001$), with a 3% decrease in likelihood of hearing impairment with each 1 cm increase in stature (Fig. 2, bottom). There was no significant heterogeneity between studies ($I^2 = 0$, $p = 0.71$).

DISCUSSION

This review identified consistent associations between birth weight and adult height with hearing in adulthood in human observational studies with low-to-moderate risk of bias. In meta-analysis of two studies, within the normal range of birth weight (2.5 to 4.5 kg), smaller birth weight was associated with hearing impairment in adulthood. Shorter adult height was consistently associated with hearing impairment in meta-analysis

TABLE 2. Studies reporting associations between adult height and adult hearing

First Author, Publication Year	Population; Setting	Sample Size, Gender, and Age	Exclusion Criteria	Study Design	Early Life Exposures	Hearing Outcome	Results
Alexsson et al. (1994)	Army conscripts, Sweden	N=500, randomly selected subsample from the Western region of Sweden; aged ~18 yrs	Certain physical deficiencies or mental defects' that are a bar to military service	Cross sectional	Adult body height	Pure tone audiometric hearing impairment (>20 dB HL in one or both ears between 250 and 8000 Hz).	Short stature was associated with hearing loss. Relative risk for hearing loss 1.84 (1.04–3.25) for those ≤170 cm in height compared with those between 169 and 189 cm in height. Those ≥190 cm in height were no different to those between 169 and 189 cm in height (RR 0.79; 0.21–2.96). Adjusted for family history of hearing loss, smoking, noise exposure history (occupation-related, music, leisure activities, firearm use).
Barrenäs et al. (2005a)	Army conscripts and noise exposed employees (street cleaners, metal workers, road constructors), Sweden	Army conscripts: n=500; 100% male; aged ~18 yrs. Includes data previously reported by Axelsson et al. (1994). Noise exposed employees: n=483; 100% male; aged between 20 and 64. Mean ages and distributions. not reported	None reported	Cross sectional	Adult body height	Pure tone audiometric hearing impairment (>20 dB HL over 500 Hz to 6 kHz in both ears).	Hearing loss twice as common in conscripts <170cm than those >170cm in height (OR 2.2; 1.2–4.0). Interaction with height and age; height and hypertension in employees (less impact in taller employees). Only *p* values reported. Conscripts: adjusted for age, family history of hearing loss, smoking, noise exposure history (occupation-related, music, leisure activities, firearm use). Employees: adjusted for age, hypertension, diabetes, smoking.
Barrenäs et al. (2005b)	Army conscripts, Sweden	N=245,092; 100% male; aged ~18 yrs.	Multiple birth, non-nordic background	Longitudinal follow-up of a birth cohort	Adult body height	Pure tone audiometric hearing impairment (>20 dB HL at 2, 4, and 6 kHz (mid frequency) and 1 and 2 kHz (high frequency) in the poorer ear).	Adult height <–2 SD associated with increased odds of high (OR 1.50; 1.31–1.71) and mid frequency hearing (OR 1.39; 1.11–1.73) (versus –2 to 2 SD range). Adjusted for birth length, head circumference, birth weight, gestational age and BMI.
Batty et al. (2017)	Population sample of adults, United Kingdom	N=4398; %male not reported; aged >50 yrs. Mean age not reported.	None reported	Longitudinal	Adult body height	Pure tone audiometric hearing screen (>20 dB HL at 1kHz or >35 dB HL at 3 kHz in the better ear).	Taller height associated with reduced odds of hearing impairment (OR 0.75; 0.59–0.95; highest vs lowest quintile). Adjusted for age, sex, IGF1, smoking status, BMI, cognitive function, educational level, physical activity, self rated health and self rated hearing at baseline.
Burr et al. (2005)	Adults from a representative population sample of people in employment, Denmark	N=7221 (cross sectional) N=4610 (longitudinal); aged 18 to 64 yrs.	Non-nordic ethic origin, head injury, missing data	Cross sectional; 5-yr longitudinal	Adult body height	Self-reported hearing loss; "Do you feel you have reduced hearing to such an extent that you feel it is difficult to follow a conversation between several people without using a hearing aid?"	Height associated with hearing loss in multiple regression stratified by sex. For males, OR for hearing loss for very short (≤172 cm) versus very tall (≥187 cm) males was 1.28 (0.84–1.95). Risks were higher for females: OR for very short (≤160 cm) females versus very tall (≥173 cm) was 1.89 (1.07–3.36). ORs for height were higher among those born before 1951. No relation between height and incident self-reported hearing loss. Adjusted for age, occupational noise exposure and smoking.

(*Continued*)

TABLE 2. Continued.

First Author, Publication Year	Population; Setting	Sample Size, Gender, and Age	Exclusion Criteria	Study Design	Early Life Exposures	Hearing Outcome	Results
Dawes et al. (2015)	Adults, United Kingdom	N=144,404; 45.5% male; aged 40 to 69 yrs.	None reported	Cross sectional	Adult body height	Speech-in-noise recognition threshold (signal-to-noise ratio) in the better ear.	Adult height associated with hearing (β −0.06, $p <$ 0.001). No association with 4-yr change in hearing. Adjusted for sex, age, social economic status, education level, smoking, cardiovascular disease, diabetes, hypertension, cholesterol, maternal smoking.
Sayer et al., (1998)	Adults born in Hertfordshire between 1920 and 1930, United Kingdom	N=717 (57% male); average age 67.5 yrs	None reported	Longitudinal follow-up of a birth cohort	Adult body height	Pure tone audiometric threshold (frequency range not reported)	Height reported as being an independent predictor of hearing. No statistics reported. Adjusted for age, sex, social class and adult height

BMI, body mass index; IGF1, insulin-like growth factor-1; OR, odds ratio; RR, relative risk.

of four studies. Associations with hearing and birth weight/adult height support the possibility that nutritional and environmental factors in early life have a critical effect on hearing function in adulthood. Early life factors may be major determinants of levels of hearing impairment in the population as well as cognitive function in childhood (Shenkin et al. 2004) and adulthood (Grove et al. 2017) and risk of dementia (Borenstein et al. 2006). Shared effects of early life factors on cognition and hearing function might explain why hearing loss is associated with poorer cognitive function and with risk of dementia (Livingston et al. 2020; Loughrey et al. 2018). Although associations are modest in size, the effect of early life factors is universal; exposures are not limited to population subgroups. Early life factors may therefore be major determinants of levels of hearing loss within adult populations (Rice & Barone 2000). Small shifts in the mean level of function within a population have a dramatic effect on the numbers of people that fall within the range of clinical impairment. In relation to cognitive function, for example, a decrease in mean population IQ of 5 points within a standard distribution doubles the number of people with an IQ <70 (Rice & Barone 2000). The effects of early life factors are a research priority in relation to noncommunicable diseases and in relation to cognitive impairment (European Parliament 2011; Hendrie et al. 2006). The effect of early life factors on hearing impairment may warrant similar attention.

Reducing rates of low birthweight internationally is a key objective of the WHO (World Health Organization 2014), although rates of low birth weight remain stubbornly high: a worldwide prevalence of 14.6% of live births in 2015, with 91% of these from low- and middle-income countries (Blencowe et al. 2019). A complex range of factors interact to affect birth weight, including maternal nutritional status, very young (especially less than 16 years of age) or older maternal age (greater than 40 years), multiple pregnancy, obstetric complications, chronic maternal health conditions (e.g., high blood pressure during pregnancy, anemia), and maternal infections (e.g., malaria, as well as bacterial and viral infections) (Blencowe et al. 2019; Johnson et al. 2017). Other environmental and lifestyle risks include air pollution, alcohol and tobacco and illicit drug use, with exposure to tobacco smoke (both active smoking and passive exposure) the largest attributable risk in one high income country (Wales; Johnson et al. 2017). Risks are interrelated and most prevalent within more deprived populations nationally and internationally. Improving early development (and subsequent outcomes including, perhaps, population levels of hearing impairment) requires multicomponent interventions.

It may be that associations with birth weight and height with adult hearing are due to confounding with socioeconomic or birth trauma factors, despite attempts to control for possible confounders. Lack of control for a full range of potential confounders is a limitation of previous studies and of the meta-analysis presented in this review. But there are experimental data from animal studies (Rice & Barone 2000) consistent with human observational data suggesting an impact of early life factors on adult hearing function. Various mechanisms have been suggested for a direct causal impact of early life factors on hearing, including undernutrition affecting development (Barker 2004), alterations in gene expression (Egger et al. 2004; Provenzano & Domann 2007), the HPA-axis (Canlon et al. 2003), or growth factors (Lassale et al. 2017; Varela-Nieto et al. 2013). Early life factors have also been shown to impact susceptibility to

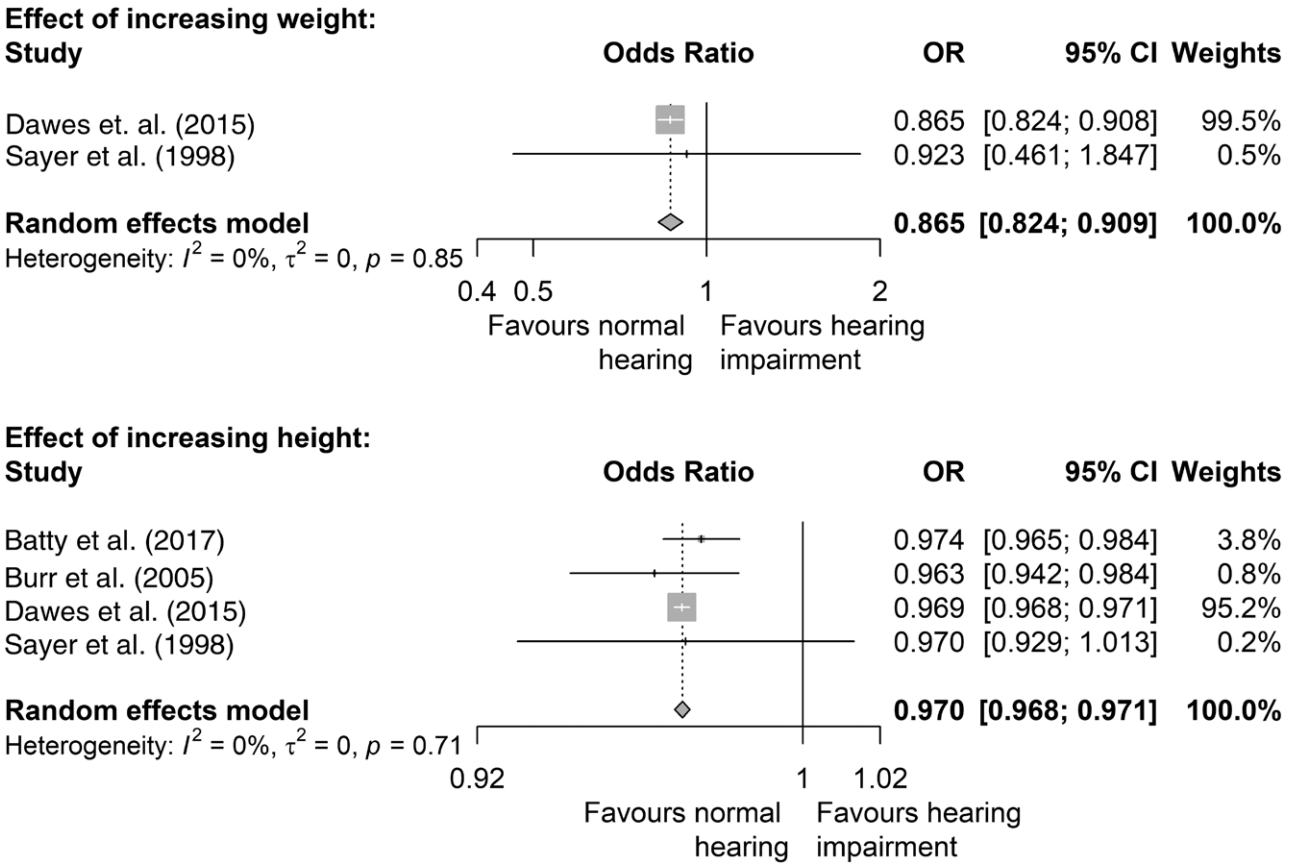

Fig. 2. Forest plots for two-step individual patient data meta-analysis of the association between birth weight (top) and adult height (bottom) with adult hearing. OR indicates odds ratio.

cardiovascular disease and diabetes (Barker 2004). Diabetes and cardiovascular disease may increase likelihood of hearing loss (Helzner et al. 2011; Horikawa et al. 2013). Although some studies controlled for these health factors (Barrenäs et al. 2005a; Batty et al. 2017; Dawes et al. 2015), the impact of early life factors on hearing may be via increased susceptibility to cardiovascular disease and/or diabetes.

In relation to birth weight, different mechanisms may affect hearing function according to the range of birth weight. Numerous studies reported that prematurity, low and very low birth weight are associated with poorer hearing (Arpino et al. 2010). Two studies in this review reported poorer hearing associated with low birth weight only (Barrenäs et al. 2005b; Olsen et al. 2001). There is also some literature showing poorer developmental outcomes for large babies (i.e., >90th or 97th percentile; Xu et al. 2010). Large birth size is associated with placental dysfunction, maternal obesity, and maternal diabetes (Langer & Mazze 1988). Dawes et al. (2015) reported a nonlinear relationship with birth weight and adult hearing; very small and very large babies had the poorest hearing in adulthood. Within the normal range of birth weight (10th to 90th percentile), increasing birth weight was associated with better hearing. In the present review, meta-analysis supported an association with normal range birth weight and adult hearing impairment. The effects of birth weight on hearing may therefore not be restricted to low or large birth weight but include the normal range of birth weight. Analysis of developmental outcomes with birth weight should ideally be corrected for gestational age and parental body size to reliably index growth restriction (Robinson et al. 2000). Most studies in this review did not correct for these factors.

Our review identified that no study reported examining associations with early life factors and adult hearing at different points in life. Effects of early life factors were observed for studies that included only young males and in studies with middle-aged and older adults. Available evidence therefore suggests a persistent impact of early life factors on hearing across the life course. Limited evidence from lower powered longitudinal analysis in two studies did not find any association between height and changes in hearing (Burr et al. 2005; Dawes et al. 2015).

Limitations

All studies in this review were conducted within relatively affluent UK or Scandinavian populations well served by medical and social care systems. Future research should investigate the impact of early development on rates of hearing impairment in low- and middle-income populations, where one might expect even higher levels hearing impairment attributable to early life factors.

Studies in this review used self-reported hearing, pure tone audiometric thresholds and speech recognition in noise performance. Use of different indexes of hearing may limit comparisons between studies. However, the various measures of hearing correlate strongly with each other (Nondahl et al. 1998; Smits et al. 2004). The strong correlation between the various indexes of hearing facilitates comparison and meta-analysis based on hearing impairment status. Studies did not distinguish between

hearing loss of sensorineural or conductive origin. As prevalence of conductive hearing loss is around 1% of people aged over 65 (Homans et al. 2017), we assume that the associations reported in this review pertain predominantly to hearing loss of sensorineural origin.

As noted earlier, a limitation of this study was the inability to control for the full range of potential confounders for the relationship between adult height or birth weight and hearing impairment in adulthood. Studies in the narrative review adjusted for a wide range of potential confounds including sex, age, ethnic background, gestational age, mothers age, parity, occupational status, marital status, social economic status, education level, noise exposure history (occupation-related, music, leisure activities, firearm use), smoking, cardiovascular disease, diabetes, hypertension, cholesterol, and maternal smoking. Several studies were conducted with samples that were homogenous according to age and/or ethnicity (e.g., 18-year-old Swedish males), minimizing potential confounds. Unfortunately, due to the requirement to harmonize data sets and the lack of available data across studies, the studies included in the meta-analyses were only controlled for age at testing and sex. Future meta-analyses should consider a broader range of confounders. Consistently controlling for a core set of factors which may affect hearing would facilitate future meta-analyses. Furthermore, only two studies provided adjusted odds ratios for the effect of weight and four for height. While this meant that only small numbers of studies were pooled, the total number of subjects included was very large and the use of gold-standard individual patient data meta-analysis means that the results provided may be more reliable than any single study alone. Although subject to critical limitations, the robust two-step patient-level analysis of large numbers of people across studies facilitates comparison of the consistency and size of associations between early life factors and adult hearing impairment across studies. Combined with the narrative review, the meta-analysis suggests early life factors are a critical determinant of hearing loss at the population level. The limitations identified above mean that research to date is suggestive rather than definitive. The implicit goal in writing this review was to stimulate research that addresses these limitations.

CONCLUSIONS

Hearing impairment is a top cause of burden due to years lived with disability and a major public health problem. Emerging evidence suggests that adverse prenatal and early childhood developmental factors are major determinants of population levels of hearing impairments in adults. Future research and public health attention should therefore focus on prevention of hearing impairment in adulthood by optimizing development early in life.

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P. D., J. N., P. G., C. O., M. B., and J. E. conceived and designed the study. Data were acquired, analyzed, and interpreted by P. D., J. N., P. G., C. O., M. B., and J. E. P. D., N. J., and P. G. drafted the article. All authors critically revised the article for important intellectual content.

The authors declare no other conflict of interest.

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