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Associations of Retinal Vessel Caliber With Hearing Status in Childhood and Midlife

A Cross-Generational Population-Based Study

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IMPORTANCE Microvascular phenotypes, which can be assessed using retinal imaging, may be informative about the life course pathogenesis of hearing loss.

OBJECTIVE To investigate whether differences in retinal vessel caliber (specifically wider venules and narrower arterioles) are associated with hearing threshold and hearing loss in mid-childhood and midlife.

DESIGN, SETTING, AND PARTICIPANTS A population-based cross-sectional study (Child Health CheckPoint) was nested within the Longitudinal Study of Australian Children. A total of 1281 children and 1255 attending parents were assessed using retinal microvasculature and air conduction audiometry data at a main assessment center in 7 large cities in Australia.

MAIN OUTCOMES AND MEASURES Air conduction audiometry was used to calculate the high Fletcher index (mean threshold of 1, 2, and 4 kHz), and bilateral hearing loss was defined as a high Fletcher index greater than 15 dB hearing level in the better-hearing ear. Retinal arteriolar and venular caliber were measured from fundus photographs using validated computer-based software. Linear and logistic regression quantified the associations of retinal vessel caliber with hearing threshold and hearing loss, respectively.

RESULTS Of the 1281 included children (mean age, 11.4 years; 49.1% boys), the mean (SD) high Fletcher index was 7.9 (5.8) dB hearing level. Of the 1255 included adults (mean age, 43.8 years; 86.6% women), the mean (SD) high Fletcher index was 13.0 (6.8) dB hearing level; 109 of 1281 children (8.5%) and 328 of 1255 adults (26.1%) had hearing loss. In adults, each 1-SD (18.6-μm) wider retinal venular caliber (worse) was associated with higher (worse) hearing threshold at lower individual frequencies (eg, 2 kHz: β = 0.63; 95% CI, 0.10-1.17) and overall high Fletcher index (eg, 2 kHz: β = 0.52; 95% CI, 0.07-0.96), as well as a 1.20-fold (95% CI, 1.03-1.40) higher odds of hearing loss. In children, patterns of venular associations were similar but smaller and less certain. Narrower retinal arteriolar caliber (worse) was associated with a 1.16-fold (95% CI, 1.00-1.37) higher odds of hearing loss in adults (per 1-SD [14.0-μm] narrower arteriolar caliber) but not in children.

CONCLUSIONS AND RELEVANCE Adverse retinal microvascular characteristics are associated with hearing loss by midlife, with venular associations possibly emerging by age 11 to 12 years. Microvascular health may contribute to the pathogenesis of hearing loss across the life course, warranting replication and mechanistic studies to inform causal inference and prevention efforts.

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 392

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Hearing loss is the most prevalent sensory disability, with its prevalence increasing over time and with advancing age.[1-3] Like other noncommunicable diseases, hearing loss may have early life origins,[4,5] and the development of timely interventions (eg, therapy for cytomegalovirus infection in the early weeks of life) may have important benefits.[6] This requires population-based data for an individual over time or across generations to understand when risk factors for hearing loss begin to emerge during the life course.[7] To our knowledge, such studies are lacking, and although genetics, ototoxic drugs, and noise exposure are the most studied risk factors for hearing loss, the biological mechanisms underlying most hearing loss are still poorly understood.

A growing body of evidence suggests that microvascular changes may contribute to hearing loss. The stria vascularis, a highly vascularized region located in the cochlear microcirculation, is the metabolic energy source underlying cochlear function.[8] Histopathologic studies show that patients with age-related hearing loss have increased thickness of vessel walls of the strial capillaries and decreased numbers of strial vessels compared with those with normal hearing.[9] This is thought to augment strial atrophy and cause degeneration of hair cells by alteration of the endolymph composition.[10]

The ability to measure many aspects of the microvasculature now provides opportunities to study its associations with hearing status. Retinal photography is a noninvasive method of investigating the retinal microvasculature. Because the retinal microvasculature shares similar anatomic and physiologic properties with the microvasculature elsewhere in the body,[11] it is a widely used surrogate marker for systemic microcirculation in population-based studies.[12,13] Many studies have shown that adverse retinal microvascular characteristics (eg, narrower arterioles, wider venules) are associated with cardiovascular risk factors (eg, obesity, hypertension, type 2 diabetes),[14-16] which are also risk factors for hearing loss.[17,18] A cohort study of 10 470 adults aged 45 to 64 years[14] showed that participants with wider retinal venules or narrower retinal arterioles were more likely to have higher systolic blood pressure, total cholesterol level, and body mass index over a mean follow-up period of 16 years. A participant-level meta-analysis of 5 cohort studies[19] showed that wider retinal vessel caliber was associated with risk of type 2 diabetes (per 1-SD wider venular caliber; pooled hazard ratio, 1.09; 95% CI, 1.02-1.15). Furthermore, some genes (eg, Norrin and Frizzled-4)[20] are known to play a central role in the vascular development of both the retina and stria vascularis. These studies support the hypothesis that abnormalities in retinal microcirculation may be correlated with abnormalities in cochlear microcirculation.[20]

To our knowledge, only 1 population-based study has reported associations of retinal microvasculature with hearing loss. In the Blue Mountains Hearing Study,[21] older adults (older than 54 years) with retinopathy (a sign of retinal microvascular damage) were twice as likely as those without to have lower-frequency hearing loss greater than 40 dB hearing level (HL) across frequencies of 0.5, 1, and 2 kHz after excluding persons with type 2 diabetes. To our knowledge, there are no analogous observational studies of participants in childhood or midlife that would be informative regarding when this association emerges and whether it progresses with age. Last, little is known about the association of more subtle microvascular differences (eg, retinal vessel caliber) with hearing loss, which may be valuable for understanding the pathogenesis of early hearing loss.

The Australian population-based cross-sectional Child Health CheckPoint study[22] provides a unique opportunity to address these evidence gaps in parent-child pairs with children aged 11 to 12 years. Therefore, we aimed to determine if retinal arteriolar and venular calibers were associated with (1) the range of hearing thresholds and (2) hearing loss in mid-childhood and midlife.

Key Points

Question Are differences in retinal vessel caliber associated with hearing threshold and hearing loss in mid-childhood and midlife?

Findings In this population-based cross-sectional study of 1281 children and 1255 adults, wider retinal venules and narrower retinal arterioles were associated with hearing loss by midlife, with venular associations possibly emerging by age 11 to 12 years.

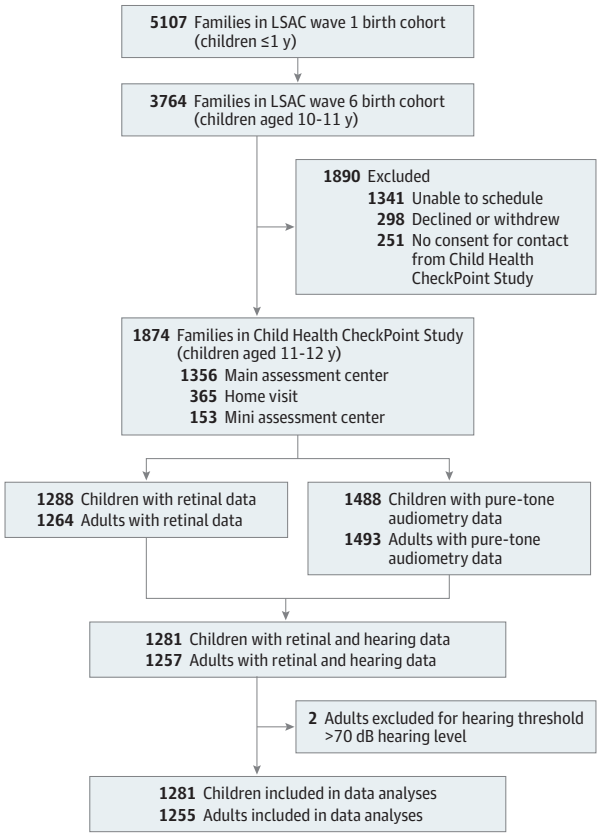
Meaning Microvascular health may contribute to the pathogenesis of hearing loss across the life course, warranting replication and mechanistic studies to inform causal inference and prevention efforts.

Methods

Study Design and Participants

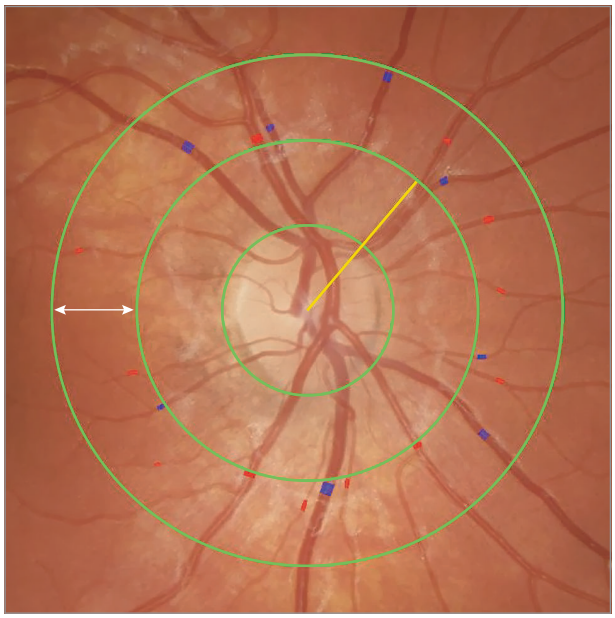
The Child Health CheckPoint study was a cross-sectional population-based substudy nested within the Longitudinal Study of Australian Children (LSAC).[23,24] In 2004, LSAC used a 2-stage random-sampling framework clustered by state, urban/rural split, and postcode to recruit a nationally representative sample of 5107 infants 1 year and younger (birth cohort).[23] Since then, LSAC has conducted follow-up of children and their families biennially. The response rate to the initial mailed invitation in 2004 was 57.2% (5107 of 8921), of whom 73.7% (3764 of 5107) were retained for wave 6 in 2014.[25] The LSAC interviewers obtained written informed consent at the wave 6 interview to give contact details to CheckPoint, which was open to all retained birth cohort children aged 11 to 12 years and 1 attending parent for each child between LSAC's wave 6 (2014) and wave 7 (2016).The Royal Children's Hospital Human Research Ethics Committee and the Australian Institute of Family Studies Ethics Committee approved the study. Parents provided written consent, and children gave verbal assent. Although we did not complete a checklist for the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines, all STROBE elements are contained within this article.

Figure 1. Participant Flow Diagram



LSAC indicates Longitudinal Study of Australian Children.[23]

Figure 2. Retinal Fundus Photograph



Photograph was assessed quantitatively using Integrative Vessel Analysis software (IVAN; University of Wisconsin). The venules (blue marks) and arterioles (red marks) are identified. Green circles indicate optic disc diameters from the disc center; yellow line, center of optic disc. For each participant, a segment of each vessel within the specific area (0.5-1.0 disc diameter from the margin of the optic disc [white 2-headed arrow]) was selected by the grader for measurement. The IVAN software then estimates summary values for the mean retinal vascular caliber according to the Big-Six (revised Knudtson-Parr[27]) formula, which combines measurements of the 6 largest arterioles or venules.

Procedures

Starting in December 2014, CheckPoint contacted families to ascertain interest and booked a single appointment for parent-child pairs.The CheckPoint assessment center conducted a visit in each Australian state sequentially between February 3, 2015, and March 25, 2016.[22,26] Ultimately, 1874 families participated, equating to 36.7% and 49.8% of those originally recruited (1874 of 5107) and retained for wave 6 (1874 of 3764) of LSAC (**Figure 1**). The attending parent was determined by the family; in practice, this was usually the mother. CheckPoint offered a specialized 3.5-hour visit to a main assessment center in 7 large Australian cities. Of the 1874 families, 518 took part in a shorter assessment at a mini assessment center or home visit and did not have retinal photographs, so they were not included in our analyses. At the main assessment center, the child and parent rotated separately through multiple 15-minute assessment stations targeting health measures relevant to noncommunicable diseases. In this article, we report data from retinal photographs, audiometry, and tympanometry.

Measures

Retinal Vessel Caliber

Two optic disc–centered digital photographs (**Figure 2**) from each eye were taken using a fundus camera (EOS 60D DSLR; Canon). Details of measurement procedures have been described elsewhere.[28] Each image was graded by 1 of 4 graders, masked to participant characteristics, using the software program Integrative Vessel Analysis (IVAN; University of Wisconsin). Right eye images were selected as the first choice for scoring, and left eye images were used when right eye images were deemed ungradable. Retinal vessels were identified by the software as arterioles or venules from a specific area (0.5-1.0 disc diameter from the margin of the optic disc). Each grader then selected a segment of each vessel within this area for measurement. Diameters of all selected segments were measured automatically using IVAN software. For each participant, summary estimates of the mean retinal vessel caliber were calculated according to the revised Knudtson-Parr formula,[27] which combines measurements of the 6 largest arterioles or venules. Our intergrader and intragrader reliability ranged from 0.79 to 0.99 (95% CI, 0.47-0.99).

Audiometry

Parent and child protocols were identical, with methods reported in detail elsewhere.[29] Trained examiners performed air conduction pure-tone audiometry using a computer-based audiometer (Oscilla USB-330, version 3.3.4; Oscilla Power) with headphones (Oscilla Power), following a standardized modified Hughson-Westlake audiometric technique.[30] Testing of the first frequency (1 kHz) began at 30 dB HL; if within normal limits, testing for other frequencies began at 20 dB HL. Participants with known hearing loss removed hearing aids and/or

cochlear implant speech processors (2 children and 3 adults); testing of the first frequency then began at 60 dB HL and of successive frequencies at 20 dB HL higher than the previous frequency. For the first 143 parent-child pairs, only 3 frequencies were tested (1, 2, and 4 kHz) for each ear across an intensity range of −10 to 120 dB HL. As CheckPoint systems became faster and additional funding was sourced, testing at 8 kHz (1342 pairs) and tympanometry (1090 pairs) were successively added. We gave parents written feedback about their own and their child's hearing results; those with thresholds greater than 20 dB HL in at least 1 ear at 2 or more frequencies were advised to consider clinical audiologic assessment.

Tympanometry (Middle Ear Function)

A combined audiometer and tympanometer (TSM500; Oscilla) automatically calculated ear canal volume, middle ear pressure, and compliance during an air pressure sweep. The resulting tympanogram curve represents the movement of the middle ear system while the pressure delivered to the tympanic membrane is varied. Tympanogram results were classified as type A (normal compliance, reflecting normal middle ear function), B (no or negligible compliance), or C (normal compliance, negative middle ear pressure), with criteria and interpretation detailed elsewhere.[1] Hearing loss in combination with a type A tympanogram result was considered sensorineural. Hearing loss in combination with a type B or C tympanogram result was considered to be of uncertain origin (ie, could reflect sensorineural and/or middle ear abnormalities).

Potential confounding factors included age, sex, gestational age (in weeks), birth weight, socioeconomic position (SEP), smoking, and preexisting conditions (including any type of diabetes and hypertension); all have been associated with both hearing loss and retinal microvasculature.[31-34] Children's date of birth, sex, gestational age, and birth weight were obtained from LSAC records. In adults, self-reported date of birth and sex were acquired at the time of assessment. The SEP included parent-reported combined household income, current or most recent occupation of each parent, and highest achieved educational qualification for each parent. Each component of the score was scaled, and an unweighted mean was calculated using 3 values in a single- parent household or 5 values in a dual-parent household. The unweighted mean variable for each LSAC wave was then standardized within the wave to a mean (SD) of 0 (1). Higher scores indicate less disadvantage. In this study, we used SEP from wave 6. For adults, smoking was determined by their answer to the question, "Are you currently smoking?" For children, we created a binary variable for passive smoking exposure if the parent questionnaire recorded any smokers at home during any LSAC wave when the child was 11 years or younger. Preexisting conditions were self-reported (yes/no) by questionnaire at the CheckPoint study assessment, including diabetes and receiving medication for hypertension.

Data Management

We calculated high Fletcher index (hFI) (mean hearing threshold across 1, 2, and 4 kHz) because its range of frequencies maps most closely to the range of important speech sound frequencies.[35] We defined hearing loss as an hFI exceeding 15 dB HL in the better-hearing ear, in line with the American Speech-Language-Hearing Association criteria for slight or worse bilateral hearing loss.[36] Slight or worse hearing loss was the primary outcome measure because we were interested in early associations of retinal microvasculature with hearing loss, in keeping with a life course approach.

Statistical Analysis

We conducted linear regression analyses to examine associations of retinal vessel caliber with hearing threshold at each frequency and hFI as well as logistic regression to examine associations of retinal vessel caliber with the binary variable of hearing loss outcome (hearing threshold >15 dB HL vs <15 dB HL). For children, we adjusted analyses for age, sex, gestational age, birth weight, and SEP. For adults, we adjusted analyses for age, sex, and SEP. In sensitivity analyses, we (1) repeated all analyses for participants with type A tympanogram results only (normal middle ear function); (2) repeated adult analyses using the American Speech-Language-Hearing Association cutoff point for mild hearing loss of greater than 25 dB HL[36]; and (3) further adjusted for smoking and preexisting conditions and for parent global region of birth and indigenous (Aboriginal/Torres Strait Islander) status. All analyses were performed using Stata statistical software version 14.0 (StataCorp), with separate analyses for children and parents.

Results

Sample Characteristics

Figure 1 presents the number of participants from wave 1 of LSAC onward; 1281 children (mean [SD] age, 11.4 [0.5] years; 49.1% [630 of 1281] boys) and 1255 attending parents (mean [SD] age, 43.8 [5.0] years; 86.6% [168 of 1255] women) were included in the analyses. The sample mean SEP was 0.26 SD higher than the mean SEP for all families in LSAC wave 6 and 0.40 SD higher than the mean SEP for all 5017 families enrolled in LSAC wave 1. Mean (SD) hFI was 7.9 (5.8) dB HL for children and 13.0 (6.8) dB HL for adults, with 8.5% (109 of 1281) and 26.1% (328 of 1255) showing hearing loss greater than 15 dB HL (**Table 1**). In adults, 56 of 1255 (4.5%) had mild or worse hearing loss. The means (SDs) for retinal arteriolar and venular caliber were 159.1 (11.9) µm and 230.7 (16.6) µm, respectively, in children and 151.1 (14.0) µm and 218.9 (18.6) µm in adults.

Associations of Retinal Vessel Caliber With Hearing Acuity

In adults, each 1-SD (18.6-µm) wider retinal venular caliber was associated with higher (worse) hearing threshold (dB HL) at lower individual frequencies (eg, 2 kHz: β = 0.63; 95% CI, 0.10-1.17) and overall hFI (eg, 2 kHz: β = 0.52; 95% CI, 0.07-0.96) but not with higher individual frequencies (**Figure 3** and **Table 2**). Similar but attenuated patterns were seen for children's hearing threshold, with greatest clarity at 1 kHz per 1-SD (16.6-µm) wider venular caliber (β = 0.47; 95% CI, 0.03-0.92). Each 1-SD (18.6-µm) wider venular caliber also had a 1.20-fold (95% CI, 1.03-1.40) higher odds of adult hearing loss as measured by the hFI, mainly driven by hearing loss at lower

frequencies (1 kHz: odds ratio [OR] = 1.20; 95% CI, 1.03-1.41; 2 kHz: OR = 1.23; 95% CI, 1.04-1.45). Again, similar but smaller and less precise associations were noted for children's hearing loss (Table 2).

In adults, each 1-SD (14.0-µm) narrower retinal arteriolar caliber was associated with a higher odds of hearing loss at lower individual frequencies (1 kHz: OR =1.19; 95% CI, 1.02-1.39; 2 kHz: OR = 1.18; 95% CI, 1.00-1.39) and overall hFI (OR = 1.16; 95% CI, 1.00-1.37). However, retinal arteriolar caliber was not associated with adult thresholds or with child hearing loss or thresholds.

Sensitivity Analyses

Similar patterns of associations were found for participants with type A tympanogram results only (eTable 1 in the Supplement) and for adults with hearing loss greater than 25 dB HL (eTable 2 in the Supplement). These similar patterns were also found when further adjusting for smoking and preexisting conditions (eTable 3 in the Supplement) and for parent global region of birth and indigenous status (data available on request).

Discussion

Principal Findings

In contemporaneous population-based samples, we found that wider retinal venules and narrower retinal arterioles—both considered adverse microvascular changes—were associated with poorer hearing by midlife for lower frequencies and hFI (composite threshold most relevant to speech frequencies) but not for higher frequencies. The association of retinal venular caliber with hearing acuity may start to emerge by midchildhood, with 1-SD wider venular caliber increasing the odds of hearing loss by 20% for adults.

Table 1. Participant Characteristics

Characteristic	Children (n = 1281)	Adults (n = 1255)
Mean (SD) age, y	11.4 (0.5)	43.8 (5.0)
Male sex, No. (%)	630 (49.1)	168 (13.4)
Mean (SD) birth weight, kg	3.4 (0.6)	NA
Gestational age, wk	39.2 (2.0)	NA
<38, No. (%)	147 (11.5)	NA
38 to <42, No. (%)	1065 (83.1)	NA
≥42, No. (%)	60 (4.7)	NA
Family socioeconomic position	0.26 (0.97)	0.26 (0.97)
Smoking, No. (%)		
Current	NA	104 (8.3)
Passive	183 (14.3)	NA
Preexisting condition, No. (%)		
Diabetes	3 (0.2)	29 (2.3)
Hypertension (while receiving medication)	NA	65 (5.2)
Mean (SD) hearing threshold, dB HL[a]		
1 kHz	10.4 (7.0)	13.7 (7.4)
2 kHz	7.7 (7.1)	12.8 (8.1)
4 kHz	5.6 (8.0)	12.7 (10.0)
8 kHz	5.0 (9.1)	14.4 (14.0)
High Fletcher index (mean of 1, 2, and 4 kHz)	7.9 (5.8)	13.0 (6.8)
Hearing loss, No. (%)		
>15 dB HL[b]	109 (8.5)	328 (26.1)
>25 dB HL[c]	10 (0.8)	56 (4.5)
Mean (SD) retinal caliber, µm		
Arteriolar	159.1 (11.9)	151.1 (14.0)
Venular	230.7 (16.6)	218.9 (18.6)

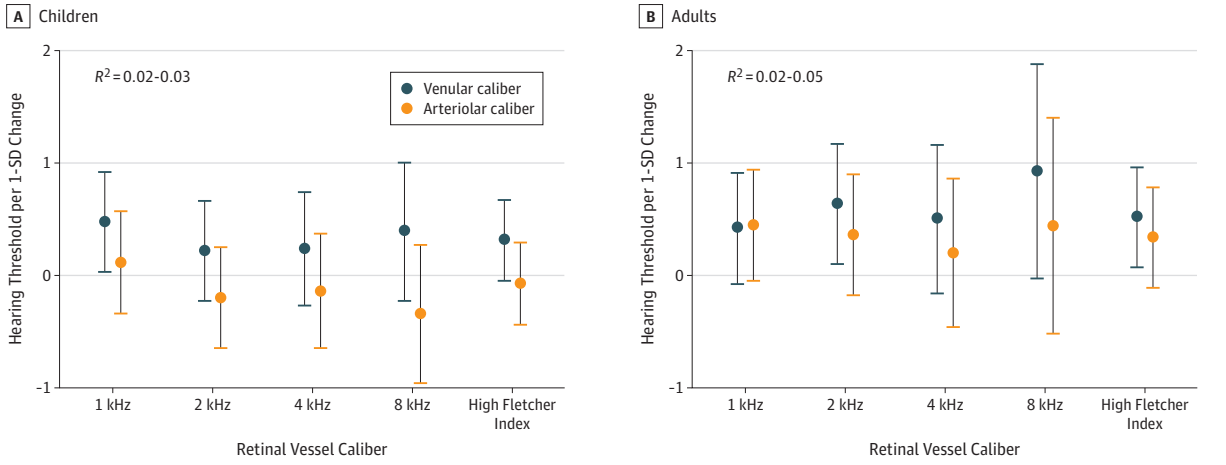
Abbreviations: HL, hearing level; NA, not applicable.

[a] In the better-hearing ear.

[b] Defined as high Fletcher index >15 dB HL in the better-hearing ear.

[c] Defined as high Fletcher index >25 dB HL in the better-hearing ear.

Figure 3. Associations of Retinal Vessel Caliber With Hearing Thresholds



A, Associations of retinal vessel caliber with hearing thresholds per 1-SD change in children, adjusted for age, sex, gestational age, birth weight, and family socioeconomic position. B, Associations of retinal vessel caliber with hearing thresholds per 1-SD change in adults, adjusted for age, sex, and family socioeconomic position. Associations were calculated using linear regression. The regression coefficient (β) represents the change in hearing threshold (dB hearing level [HL]) per 1-SD wider retinal venular caliber (or per 1-SD narrower retinal arteriolar caliber). All individual frequencies and high Fletcher index thresholds are for the better-hearing ear.

Table 2. Associations of Retinal Vessel Caliber per 1-SD Change With Hearing Acuity

Hearing Acuity	Retinal Vessel Caliber, Measure (95% CI)[a]	
	Venular per 1-SD Wider	Arteriolar per 1-SD Narrower
Linear regression[b]		
Child threshold[c]		
1 kHz	0.47 (0.03 to 0.92)	0.12 (−0.34 to 0.57)
2 kHz	0.21 (−0.23 to 0.66)	−0.20 (−0.65 to 0.25)
4 kHz	0.23 (−0.27 to 0.74)	−0.14 (−0.65 to 0.37)
8 kHz	0.39 (−0.23 to 1.00)	−0.34 (−0.96 to 0.27)
High Fletcher index	0.31 (−0.05 to 0.67)	−0.07 (−0.44 to 0.29)
Adult threshold[d]		
1 kHz	0.42 (−0.08 to 0.91)	0.45 (−0.05 to 0.94)
2 kHz	0.63 (0.10 to 1.17)	0.36 (−0.18 to 0.90)
4 kHz	0.50 (−0.16 to 1.16)	0.20 (−0.46 to 0.86)
8 kHz	0.92 (−0.03 to 1.88)	0.44 (−0.52 to 1.40)
High Fletcher index	0.52 (0.07 to 0.96)	0.34 (−0.11 to 0.78)
Logistic regression[e]		
Child hearing loss >15 dB HL[c]		
1 kHz	1.06 (0.89 to 1.27)	0.97 (0.81 to 1.16)
2 kHz	1.11 (0.87 to 1.42)	0.89 (0.69 to 1.15)
4 kHz	1.21 (0.93 to 1.57)	0.89 (0.68 to 1.19)
8 kHz	1.14 (0.90 to 1.46)	0.93 (0.71 to 1.19)
High Fletcher index	1.12 (0.89 to 1.41)	0.96 (0.76 to 1.22)
Adult hearing loss >15 dB HL[d]		
1 kHz	1.20 (1.03 to 1.41)	1.19 (1.02 to 1.39)
2 kHz	1.23 (1.04 to 1.45)	1.18 (1.00 to 1.39)
4 kHz	1.11 (0.95 to 1.30)	1.12 (0.96 to 1.32)
8 kHz	1.08 (0.92 to 1.26)	0.99 (0.96 to 1.32)
High Fletcher index	1.20 (1.03 to 1.40)	1.16 (1.00 to 1.37)

Abbreviations: HL, hearing level; OR, odds ratio.

[a] The regression coefficient (β) represents the change in hearing threshold (dB HL) per 1-SD change in retinal vessel caliber. The OR is calculated for bilateral hearing loss greater than 15 dB HL per 1-SD change in retinal vessel caliber. All individual frequencies and high Fletcher index thresholds were for the better-hearing ear.

[b] Linear regression is presented as β (95% CI) per 1-SD wider venular caliber or narrower arteriolar caliber.

[c] Adjusted for age, sex, birth weight, gestational age, and family socioeconomic position.

[d] Adjusted for age, sex, and family socioeconomic position.

[e] Logistic regression is presented as OR (95% CI) per 1-SD wider venular caliber or narrower arteriolar caliber.

Interpretation in Light of Other Studies

Our early and midlife findings are congruent with the larger associations among older adults in the Blue Mountains Hearing Study.[21] Clinically evident retinopathy was associated with more than double the rate of low-frequency hearing loss greater than 40 dB HL (OR= 2.10; 95% CI, 1.09-4.06) among adults 54 years and older),[21] contrasting with our smaller effect sizes (eg, per 1-SD wider retinal venular caliber: OR = 1.20; 95% CI, 1.03-1.40). This is not surprising because retinopathy is a sign of advanced microvascular damage. There is also indirect supporting evidence from studies examining associations of cardiovascular diseases and risk factors with hearing loss.[17,37,38] For example, in the Framingham cohort,[17] cardiovascular diseases (eg, stroke, coronary artery disease, intermittent claudication) were associated with low-frequency hearing loss (ORs ranged from 1.75 to 4.39) more than than high-frequency hearing loss (ORs ranged from 1.49 to 1.97). Similarly, the US National Health and Nutrition Examination Survey found that obesity was associated only with unilateral low-frequency hearing loss (OR = 1.9; 95% CI, 1.1-3.1) among 12- to 19-year-olds.[37] These associations in lower-frequency hearing loss are plausible, since lower-frequency sounds are transduced at the apex of the cochlea, where the blood supply is provided by distal capillaries.[17] In contrast, high-frequency hearing is believed to be most influenced by noise exposure, which is known to initially damage the outer hair cells associated with the perception of high-frequency sounds (3-kHz to 6-kHz range)[39,40] via the accumulation of reactive oxygen species and the active stimulation of intracellular stress pathways.[41]

Implications

Our findings support the theory of a life course microvascular contribution to the pathogenesis of hearing loss, especially in lower-frequency ranges. It will be valuable to conduct patient follow-up over time to establish the causal relationships of changes in microvasculature with age at hearing loss onset, rate of decline, and hearing loss trajectories.

Second, retinal venular but not arteriolar caliber was associated with hearing acuity in mid-childhood, suggesting that venular circulation may be more central to early-onset hearing loss than arteriolar circulation. To our knowledge, studies to date have suggested that retinal arteriolar and venular caliber reflect different vascular pathophysiologic processes.[42] Smaller arteriolar caliber is closely associated with elevated blood pressure. Therefore, the lack of association between retinal arteriolar caliber and child hearing acuity may reflect the low prevalence of hypertension in children. Studies of other advanced arteriolar damage signs (eg, focal arteriolar narrowing, arteriovenous nicking) could help researchers better understand the role of arterioles in child hearing loss. In contrast, larger venular caliber appears to arise from inflammation and endothelial dysfunction.[43] The associations we found between venular caliber and hearing acuity may indicate that the earliest stages of hearing decline have inflammatory origins.[44] In animal studies, inflammation stimulates the recruitment of circulating immunocytes to the cochlea.[45] These cells enter the cochlea through the postcapillary venules in the spiral ligament, whose fibrocytes function to recirculate potassium and maintain the endocochlear potential. Future population-based studies should investigate whether and how much retinal venular caliber mediates the association of inflammation with hearing loss.

Third, there is increasing interest in targeting microcirculation in the prevention and treatment of cardiovascular diseases. For example, angiotensin-converting enzyme inhibitors and calcium channel blockers may have direct beneficial associations with microvascular structure and preventing car-

diovascular morbidity.[46] In light of the findings from our study, we advocate that population-based trials of these agents in cardiovascular diseases add hearing loss as an outcome measure. Fast, high-quality hearing apps now make this much more feasible at the population level.

Strengths and Limitations

To our knowledge, we are the first to investigate with a high degree of measurement comparability the same associations in a large, population-based sample of children and adults. Assessments of the 2 generations were conducted on the same day, by the same staff, using the same equipment and protocols, and in the same order for all participants. These methodologic considerations avoid many of the potential sources of bias and unknown confounding seen in cross-generational studies. Children aged 11 to 12 years had good compliance with testing protocols[47,48] and accurate ascertainment of even slight hearing loss. Retinal vessel caliber was quantified using a previously validated computer-based technique with comparable intergrader and intragrader reliability.[49] In addition, our study goes further than previous studies by investigating the patterns (frequency-specific effects) of the associations of subtle microvascular differences with hearing loss and when in the life course these associations may emerge.

There were also limitations. First, as in other population-based studies,[37,50,51] we lacked bone conduction audiometry data owing to the strict time constrains of a whole-participant assessment, with hearing just 1 of multiple health domains measured within CheckPoint. However, our sensitivity analyses indicated that middle ear function likely had little influence on our results. Second, as with all longitudinal cohort studies, there has been significant attrition over time. Our findings may not generalize to more disadvantaged families, although adjusting for family SEP may have partly mitigated this problem. Third, retinal and audiometric data were collected at 1 time point, so we are unable to draw any inferences regarding causality. Fourth, the effect sizes of these associations were small (accounting for 3% to 9% of variance in hearing outcomes). Residual confounding from race/ethnicity, occupational noise exposure,[52] and genetic risk factors could have contributed to the associations seen.[20] However, small associations may still be important at the population level.

Conclusions

Adverse retinal microvascular characteristics are associated with hearing loss by midlife, with retinal venular associations possibly emerging by age 11 to 12 years. Microvascular health may contribute to the pathogenesis of hearing loss across the life course, warranting replication and mechanistic studies to inform causal inference and prevention efforts.

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