Early childhood undernutrition increases risk of hearing loss in young adulthood in rural Nepal

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ABSTRACT

Background: Prevalence of young adult hearing loss is high in low-resource societies; the reasons for this are likely complex but could involve early childhood undernutrition.

Objective: We evaluated preschool childhood stunting, wasting, and underweight as risk factors for hearing loss in young adulthood in Sarlahi District, southern Nepal.

Design: Ear health was assessed in 2006–2008 in a cohort of 2193 subjects aged 16–23 y, who as children <60 mo of age participated in a 16-mo placebo-controlled, randomized vitamin A supplementation trial from 1989 to 1991. At each of five 4-mo assessments, field staff measured children's weight, height, and mid-upper arm circumference (MUAC) and recorded validated parental history of ear discharge in the previous 7 d. Children were classified as stunted [<–2 *z* score height-for-age (HAZ)], underweight [<–2 *z* score weight-for-age (WAZ)], or wasted [<–2 *z* score MUAC-for-age (MUACAZ) or body mass index-for-age (BMIAZ)]. At follow-up, hearing was tested by audiometry and tympanometry, with hearing loss defined as pure-tone average >30dB in the worse ear (0.5, 1, 2, 4 kHz) and middle-ear dysfunction as abnormal tympanometric peak height (<0.3 or >1.4 mmho) or width (<50 or >110 daPa).

Results: Hearing loss, present in 5.9% (95% CI: 5.01%, 7.00%) of subjects, was associated with early childhood stunting (OR: 1.64; 95% CI: 1.10, 1.45), underweight (OR: 1.70; 95% CI: 1.18, 2.44) and wasting by BMIAZ (OR: 1.88; 95% CI: 1.19, 2.97) and MUACAZ (OR: 2.14; 95% CI: 1.47, 3.12). Abnormal tympanometry, affecting 16.6% (95% CI: 15.06%, 18.18%), was associated with underweight (OR: 1.46; 95% CI: 1.16, 1.84) and wasting by BMIAZ (OR: 1.80; 95% CI: 1.32, 2.46) and MUACAZ (OR: 1.42; 95% CI: 1.10, 1.84), but not stunting (OR: 1.18; 95% CI: 0.93, 1.49) in early childhood. Highest ORs were observed for subjects with both hearing loss and abnormal tympanometry, ranging from 1.87 to 2.24 (all lower 95% CI >1.00).

Conclusions: Early childhood undernutrition is a modifiable risk factor for early adulthood hearing loss. *Am J Clin Nutr* 2018;107:268–277.

Keywords: undernutrition, hearing loss, Nepal, stunting, wasting, low-resource settings, nutrition

INTRODUCTION

Hearing loss ranks as the fourth leading cause of years lived with disability, and 80% of the estimated 1.1 billion people living with hearing loss globally reside in low- and middle-income countries (1). Children with hearing loss are at risk for speech, language, and cognitive delays (2–5), decreased school performance (6–9), and increased likelihood of limited employment opportunities as adults (10, 11). Where examined in South Asia, the prevalence of school-aged to adolescent and early adult hearing loss ranges from 14.2% (95% CI: 7.9%, 26.4%) in males and 9.1% (95% CI: 4.9%, 17.4%) in females aged 5–19 y to 27.7% (95% CI: 16.1%, 45.1%) in men and 18.9% (95% CI: 10.6%, 33.3%) in women aged 20–34 y (12). Taken together, these estimates suggest that >116 million young people in the region are hearing impaired (12). However, the epidemiology, causation and preventable pathways to hearing loss remain poorly characterized and prevention a virtually unattended public health priority (13).

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Abbreviations: BMIAZ, BMI-for-age *z* score; CMV, cytomegalovirus; HAZ, height-for-age *z* score; MUAC, mid-upper arm circumference; MUACAZ, mid-upper arm circumference–for-age *z* score; PTA, pure-tone average; SES, socioeconomic status; WAZ, weight-for-age *z* score.

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Micronutrient deficiencies that often coexist with generalized undernutrition at critical stages of development have been linked to hearing impairment. Missing from the literature is a rigorous exploration of the risk of hearing loss imposed by generalized undernutrition in early life (13). Undernutrition, expressed as stunted linear growth and suboptimal weight for a child's age, remains the dominant form of childhood malnutrition throughout rural South Asia. The prevalence of stunting, wasting, and underweight in South-Central Asia is 37.8%, 16.1% and 31.8%, respectively, affecting an estimated 162 million children and accounting for substantial preschool morbidity and mortality (14). While there are plausible mechanisms by which chronic protein and energy deprivation during development may interfere with ear formation and function in fetal and early postnatal stages (15–17), virtually no population evidence exists to associate early childhood wasting, stunting, or their joint expression as underweight with risk of later-life hearing loss.

In this paper, we report associations between early childhood undernutrition and risks of hearing loss and middle-ear dysfunction in a cohort of young adults in rural southern Nepal, where high burdens of early childhood wasting, stunting (18,19), and ear infections (20) coexist with hearing loss in later childhood and adulthood (20,21). During their preschool years, this cohort participated in a randomized trial of vitamin A supplementation that also assessed nutritional status by anthropometry (18). Our primary hypothesis was that stunting, wasting, and underweight during the preschool-aged years would be positively associated with hearing loss, as measured during a 16-y follow-up study in early adulthood. The presence of such a longitudinal association would be consistent with a hypothesis that adequate nutrition early in life could help reduce hearing disability in later life, providing an as-yet little appreciated argument for preventing childhood malnutrition.

SUBJECTS AND METHODS

This study was carried out from 2006 to 2008 in the population-dense district of Sarlahi in the plains of southern Nepal, an area resembling in ecological, cultural, and demographic terms the greater Gangetic floodplain of South Asia. Participants were 2193 young adults aged 16–23 y who as preschool-aged children participated in a cluster-randomized vitamin A supplementation trial between 1989 and 1991 (Nepal Nutrition Intervention Project-1, NNIPS-1) (18). Details of the original trial design and methods have been previously described (18). Briefly, 261 administrative wards in 29 contiguous Village Development Communities in Sarlahi District were randomized for preschool children to receive every 4 mo either vitamin A or placebo supplements, containing either 200,000 IU or 300 IU (placebo) of vitamin A, respectively. Every 4 mo during the 16-mo trial, children's weight, height, and mid-upper arm circumference (MUAC) were measured, and a validated parental history of ear discharge in the previous 7 d was recorded, with multiple positive weekly histories interpreted as individual episodes (19, 22). Household socioeconomic status and demographic information were recorded at the second 4-mo household visit. Socioeconomic variables included asset (e.g., radios) and land ownership, drinking water source, house construction materials, and household size. Literacy status, education, and occupation of the head of the household were also recorded.

In a subsample of 40 wards, randomly and equally sampled from 4 quadrants of the study area to obtain geographic balance across the ~200 km^2 study area, parents or guardians brought their children to a central site in their community for an enhanced protocol of anthropometry, ocular, and ear health assessments. Baseline measures included the following: *1*) standing height for children ≥24 mo of age or recumbent length for children 0–23 mo, read to the nearest 0.1 cm on a steel tape attached to a wooden board with a foot plate and sliding head block (Shorr Productions); *2*) weight, with children lightly clothed or naked, read to the nearest 0.1 kg on a hanging spring scale (Salter Ltd); and *3*) left MUAC read to the nearest 0.1 cm measured using a Zerfas insertion tape (23, 24). All measures were repeated at each subsequent 4-mo visit.

Census and residence status update survey

A follow-up health and nutritional status assessment was conducted in this trial in 2006–2008. An initial census was carried out between June and August 2006 to update vital and residential status of cohort subjects who were recorded as alive at the end of the original NNIPS-1 trial in 1991. Subjects from the original subsample of 40 wards were considered to be eligible to be visited for the follow-up study if they were found to be living in their original home or tracked to another residence within the larger NNIPS study area, regardless of their physical presence on the day of the census.

Ear health and hearing study

Details of the present ear health study protocol have been previously described (27). Eligibility was restricted to adolescents and young adults in the 40-ward subcohort who were enrolled at the first (baseline) visit of the original trial when <5 y of age, exited the trial alive in 1991, and were reported to be resident in the study area in the 2006 census. Subjects were excluded from analysis if their original trial records lacked baseline anthropometry data (height, weight, and MUAC). The follow-up ear health study consisted of 2 activities on separate days: a household socioeconomic survey carried out by trained interviewers, and an ear examination and screening test for hearing and middle-ear dysfunction, which was performed by a clinically trained team. Verbal consent was obtained from subjects aged ≥18 y. Assent from subjects plus verbal consent from parents or guardians were obtained for individuals aged <18 y, unless subjects were married in which case their consent was obtained as emancipated minors.

Clinical ear examinations and hearing tests were conducted by 2 trained technicians at a convenient site in each participant's community (20). An additional consent, specific to the hearing disorders assessment protocol, was obtained before the exam. The tympanic membrane was examined using a lighted otoscope (HEINE mini 2000). The presence of cerumen impaction, defined as >80% canal occlusion by ear wax, was recorded. Audiometric testing was performed using a digital audiometer (240 digital audiometer; Amplivox) with foam-tipped insert earphones (Auditory System; E-A-R). Cerumen was not removed prior to hearing assessment. In pure-tone audiometry, an individual is presented with tones at different frequencies (kHz) and intensities (measured in decibels hearing level, dB) to determine the

quietest audible sound at each frequency. The standard frequencies tested in audiometric evaluation (0.5, 1, 2, 4, 8 kHz) include the speech frequencies. Thresholds ≤25dB are considered normal (25). Participants who failed to respond to a screening tone of 30 dB in either ear at ≥1 frequency (0.5, 1, 2, 4, 8 kHz) were considered to have failed screening and proceeded to full audiometric testing to establish air conduction thresholds at 0.5, 1, 2, 4, and 8 kHz bilaterally. For those who failed to respond at the limit of the audiometer's range, the next intensity level beyond the audiometer's limit, 125 dB hearing level, was assigned for frequencies with no response (20, 26). The thresholds at 0.5, 1, 2, and 4 kHz were averaged to generate a pure-tone average (PTA). Hearing loss was defined by PTA >30 dB (0.5, 1, 2, 4 kHz) in the worse hearing ear. Background noise levels were separately measured and recorded before hearing screening (Quest 2100 Basic Sound Level Meter) and full audiometric testing (Quest 2700 Advanced Sound Level Meter with Octave Band Filter).

A portable tympanometric device (Welch-Allyn Micro Tymp 2 Tympanometer) was used to assess middle-ear health and function in this study. Tympanometry measures the volume of the external auditory canal and the compliance of the tympanic membrane (27). It is an important adjunct to pure-tone audiometry, particularly in populations that experience high prevalence of ear infections (28). Middle-ear dysfunction was defined as an abnormal tympanometric peak height (<0.3 or >1.4 mmho) or abnormal width, defined by the distance in daPa across the tympanogram at a height 50% down from the peak (<50 or >110 daPa) based on norms recommended by the manufacturer for the specific device (29). Standard calibration was applied, as the study region has an average elevation of 125 m above sea level.

Compliance

A substantial proportion of subjects listed as resident during the 2006 census were absent during the initial ear assessment. In order to raise response rates, field teams continued to revisit households of unmeasured subjects during a period of 8 mo following completion of the first set of visits in the ear health study whenever subjects were reported as having returned home by local staff or family. In addition, for a period of 2 wk in November 2007, field teams relocated to Kathmandu to assess subjects whose residence had changed to the capital city and for whom approximate addresses were available.

All completed data forms were checked for errors and attempts were made to resolve inconsistencies in the field before transmittal by vehicle to a data-processing center in Kathmandu. Upon data entry, data were again checked for errors and, if valid to do so, returned to the field for resolution.

Statistical analysis

Preschool nutritional anthropometric indicators, including height-for-age z score (HAZ), weight-for-age z score (WAZ), BMI-for-age z score (BMIAZ) and MUAC-for-age z score (MUACAZ), were expressed as SD (z) scores by comparing the anthropometric measures to age-sex specific distributions from the WHO Multicenter Growth Reference Study child growth standards (WHO Anthro, version 3.2.2) (30). Implausible z score values were coded as missing for the present study. BMI was calculated by dividing weight in kilograms by the square of height in meters. Stunting was defined by HAZ <–2, underweight by WAZ <–2, and wasting by either BMIAZ <–2 or MUACAZ <–2.

Initial analysis assessed the potential of selection bias by comparing a number of early childhood characteristics of study participants with subjects who were listed as area residents in the project's 2006 census but who, after several months of periodic checking, remained absent from home. Distributions of discreet characteristics between groups were tested for significance by a chi-square test. Risks of young adult hearing loss and middle ear dysfunction associated with early childhood nutritional status were estimated by ORs and 95% CIs derived from unadjusted logistic regression models. Statistical significance of unadjusted OR estimates (i.e., P value <0.10) guided selection of most variables for inclusion into the multivariable model. However, certain conventional demographic and socioeconomic variables were included in the risk estimation models irrespective of the statistical significance of their association with hearing loss outcomes (31). Model adequacy was evaluated using the Hosmer-Lemeshow goodness-of-fit test.

Data from both randomly assigned supplementation groups in the original trial (vitamin A or placebo) were used in this analysis. An interaction term representing the effect of supplementation was added to each final model to assess whether vitamin A supplementation modified the risk of hearing loss in young adulthood associated with baseline anthropometric indicator levels of preschool undernutrition. All analyses were conducted using SAS, version 9.3. (SAS Institute Inc.).

This study was reviewed and approved by the institutional review boards at the Institute of Medicine, Tribhuvan University, Kathmandu, Nepal and the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.

RESULTS

Follow-up of study participants

A total of 4765 children aged <5 y entered the original trial during the baseline visit from September to December 1989, of whom 4375 were recorded as alive and resident in the study area at the end of the trial (follow-up visit 7) in 1991 (**Figure 1**). Among these children, 414 did not have requisite baseline anthropometry data from the original trial. Of the 3961 remaining children, 846 reportedly moved and 129 died over the subsequent 15 y. Thus, 2986 children were reported to be resident in the study area at the time of the 2006 prestudy census, representing the target group for the follow-up ear health survey. Between the census and the ear health assessment, a period that spanned 3–13 mo, 114 additional children had moved, 16 had died, and 619 were repeatedly found to be absent for the hearing assessment. A small number of either parents or children refused to participate on the day of the ear health assessment ($n = 9$), leaving longitudinal data available for 2193 subjects, representing 50% of the subjects who were alive at the close-out of the trial ($n = 4375$) in 1991 and 73% of the study's target group ($n = 2986$) reported resident at the time of the pre-study census.

Comparability of participants and nonparticipants in hearing assessment

The ear health and hearing study did not assess all presumed survivors who exited the original trial. Thus, to evaluate

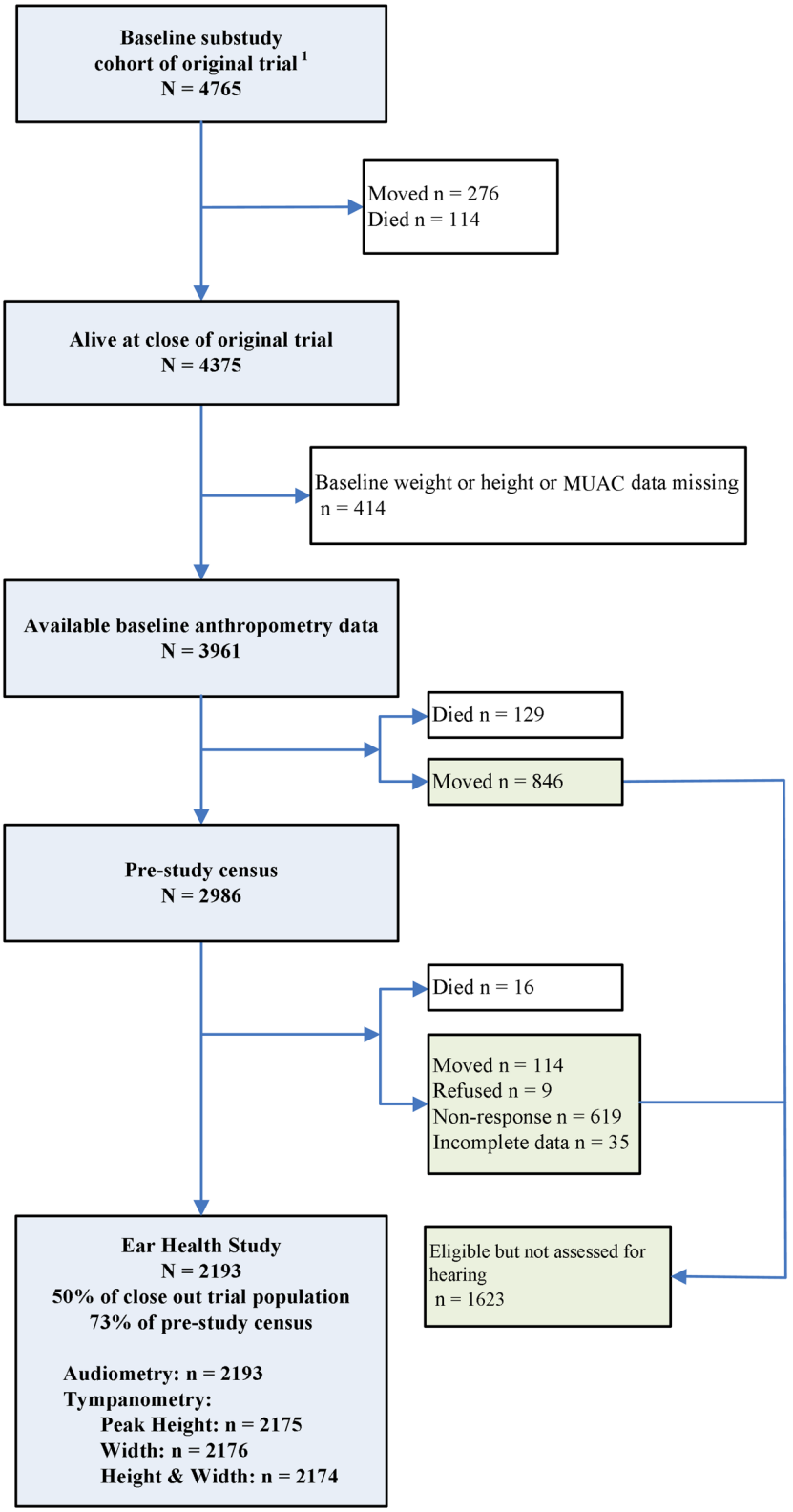

FIGURE 1 Flowchart of participants at baseline (1989) and close-out of original trial (1991), presurvey census (2006) and ear health study (2006–2008), Sarlahi Nepal. [1]Enrolled and assessed at baseline visit of trial (first of 7 total visits) from September to December 1989. MUAC, mid-upper arm circumference.

TABLE 1
Household and child characteristics during the original trial by hearing assessment status as young adults (n = 3648), Sarlahi, Nepal 2006–2008[1]

	Hearing assessed			
	Yes ($n = 2193$)		No[2] ($n = 1623$)	
	n	%	*n*	%
Household				
Literate head of household[3]	996	45.4	616	38.0
Head of household completed secondary school[4]	164	7.5	90	5.6
Head of household occupation[3]				
Farmer	1510	69.0	961	59.2
Laborer	378	17.2	381	23.5
Private, business, or government service	305	13.9	281	17.3
Higher caste[4]	479	21.8	290	17.9
>1 room in house[3]	1147	52.3	713	43.9
Tube well water source	1084	49.4	827	51.0
In-home latrine[4]	122	5.6	61	3.8
Ownership				
Land[3]	1747	79.7	1159	71.4
Watch[3]	575	26.2	350	21.6
Bicycle[3]	463	21.1	270	16.6
Radio[4]	527	24.0	339	20.9
Child				
Male gender[3]	1313	59.9	711	43.8
Age ≥12 mo at baseline[3]	1749	79.8	1385	85.3
MUAC-for-age *z* score <–2 at baseline[4]	496	23.7	420	26.8
Morbidity histories[5]				
Ear discharge	151	6.9	110	6.8
Fever	125	5.7	71	4.4
Diarrhea	72	3.3	49	3.0
Dysentery	10	0.5	7	0.4
Cough	88	4.0	66	4.1
Cough with rapid breathing	27	1.2	13	0.8

[1] 132 subjects who died after close of original trial were excluded from comparison. Baseline variables missing: literacy (0 non-assessed; 1 assessed), rooms (1 non-assessed; 6 assessed) and MUAC (101 non-assessed; 51 assessed). Interviewers asked about rapid breathing (lower respiratory tract infection), >4 loose stools/d (diarrhea), discharging ear infection or pus, high fever, and dysentery. MUAC, mid-upper arm circumference.

[2] Either moved away between 1991 and 2006 and not reported to have died ($n = 846$) or subjects who were reported resident in study area in 2006 but not found for assessment ($n = 777$).

[3] $P < 0.001$ by chi-square test.

[4] $P < 0.05$ by chi-square test.

[5] Based on having ≥3 positive weekly histories at the seven 4-mo home visits during the trial.

potential nonresponse biases, early childhood household, health, and nutritional characteristics were compared between subjects who participated in the ear health and hearing study ($n = 2193$) and those who did not for reasons of having moved or otherwise not found for assessment ($n = 1623$) (**Table 1**). Young adult participants in the ear health and hearing study were more likely than those not assessed to have been raised in households of higher socioeconomic status, reflected in head of household literacy (45.4% compared with 38.0%; $P < 0.001$), education through secondary school (7.5% compared with 5.6%; $P < 0.05$), and occupation as farmer (69.0% compared with 59.2%; $P < 0.001$). Households of participants were more likely to be from higher castes (Brahmin or Chettri) (21.8% compared with 17.9%; $P < 0.05$) and own land (79.7% compared with 71.4%; $P < 0.001$) and other assets such as watches, bicycles, and radios compared with nonparticipants (all $P < 0.001$). Subjects who participated in the study were more likely than nonparticipants to be male (59.9% compared with 43.8%) and younger in age (79.8% compared with 85.3% ≥1 y of age at the time of the baseline visit of the original trial) (both $P < 0.001$). Participants, as preschoolers, were also slightly less likely at the original baseline visit to have been wasted by arm circumference (MUACAZ <–2: 23.7% compared with 26.8%; $P < 0.05$), although general levels of early childhood illness were comparable as reported by repeated 7-d histories of symptoms of infectious morbidity, including ear discharge, throughout the original trial. This comparability in health suggests that the differences in socioeconomic and demographic status in early childhood likely had minimal influence on nutritional and infectious exposures being examined in relation to hearing loss in young adulthood. Within the ear health and hearing study cohort itself there were no significant differences in socioeconomic or demographic characteristics measured in early childhood by hearing status in young adulthood, further suggesting that early childhood demographic and socioeconomic factors had little influence on later-life hearing loss in this cohort (data not shown). All further analyses are restricted to cohort participants in the ear health and hearing study for whom the requisite risk factor data from early childhood exists.

Preschool nutritional status

Preschool nutritional status at the baseline visit of the trial was poor (**Figure 2**), reflected by low values (mean ± SD) of HAZ (–2.4 ± 1.4), WAZ (–2.0 ± 1.1), BMIAZ (–0.7 ± 1.1), and MUACAZ (–1.4 ± 0.9).

Adolescent and young adulthood hearing and tympanometry status

Of 2193 subjects assessed, 5.93% ($n = 130/2193$; 95% CI: 5.01%, 7.00%) demonstrated hearing loss. Further, a total of 16.56% ($n = 360/2174$; 95% CI: 15.06%, 18.18%) exhibited abnormal tympanometry by abnormal peak height or width, with abnormal peak height evident in 13.47% ($n = 293/2175$; 95% CI: 12.10%, 14.97%) and abnormal width in 10.29% ($n = 224/2176$; 95% CI: 9.09%, 11.64%) of subjects, respectively.

Risk of hearing loss in young adulthood by preschool nutrition status

Subjects who were malnourished (<–2 *z* for standardized indicators) as children were consistently at higher risk of being hearing impaired as young adults (**Table 2**). Hearing loss was associated with early childhood stunting (HAZ OR: 1.64; 95% CI: 1.10, 2.45), underweight (WAZ OR: 1.70; 95% CI: 1.18, 2.44), and wasting (MUACAZ OR: 2.14; 95% CI: 1.47, 3.12; BMIAZ OR: 1.88; 95% CI: 1.19, 2.97), associations that remained after adjustment for age, sex, and multiple indicators of socioeconomic status (SES) (Table 2). ORs for hearing loss with each indicator of early childhood undernutrition remained nearly the same after further controlling for ear infections with discharge (Adjusted

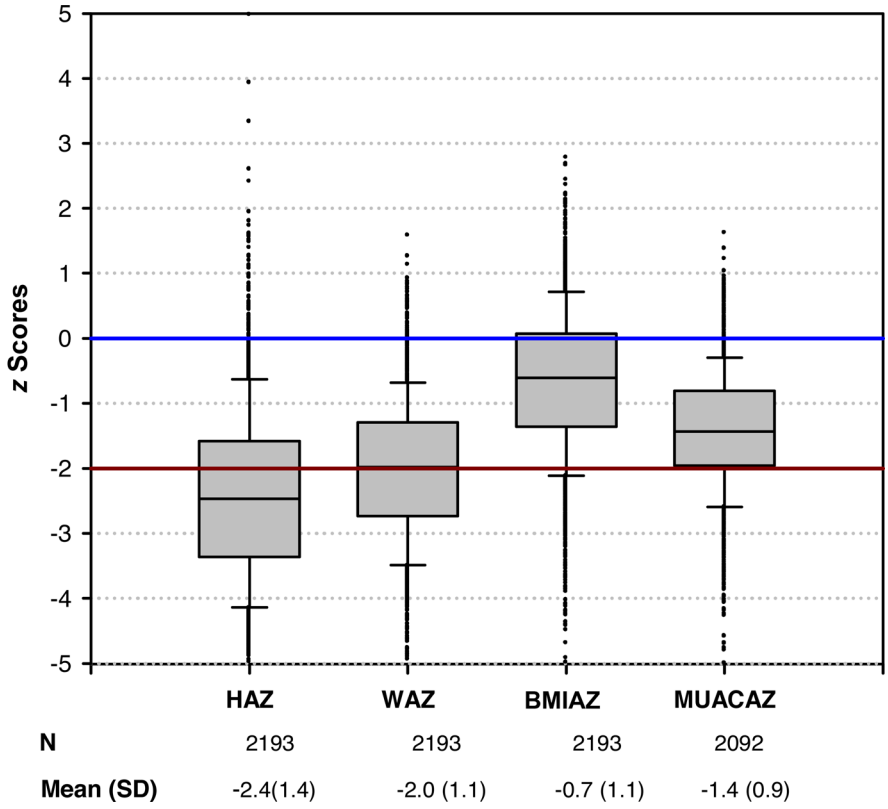

FIGURE 2 Boxplot of preschool nutritional status at baseline visit, Sarlahi, Nepal, 1989–1991. Nutritional status is described in terms of HAZ, WAZ, BMIAZ, and MUACAZ. BMIAZ, BMI-for-age *z* score; HAZ, height-for-age *z* score; MUACAZ, mid-upper arm circumference–for-age *z* score; WAZ, weight-for-age *z* score.

Model 2, Table 2), a leading early childhood cause of hearing loss (32). Tympanometry can assist in delineating whether hearing loss is sensorineural (permanent, nerve-related loss) or conductive (middle ear-related and often mediated by infection), with hearing loss independent of abnormal tympanometry more likely to be sensorineural in nature. When adjustment for abnormal tympanometry was performed, hearing loss remained associated with early childhood stunting (HAZ OR: 1.80; 95% CI: 1.13, 2.86). The hearing loss associations with underweight (WAZ OR: 1.42; 95% CI: 0.95, 2.12) and wasting (BMIAZ OR: 1.33; 95% CI: 0.77, 2.30; MUACAZ OR: 1.78; 95% CI: 1.16, 2.73) were diminished, with declines in ORs for all 3 indicators and only MUAC maintaining significance (Adjusted Model 3, Table 2). All associations between hearing loss and indicators of early childhood undernutrition remained when adjusting for cerumen impaction, which can cause temporary hearing loss (Adjusted Model 4, Table 2).

Risk of abnormal tympanometry in young adulthood by preschool nutrition status

Middle-ear dysfunction, reflected by abnormal tympanometry, was not associated with early childhood stunting (HAZ OR: 1.18; 95% CI: 0.93, 1.49) but was associated with underweight (WAZ OR: 1.46; 95% CI: 1.16, 1.84) and wasting by both BMI and MUAC (BMIAZ OR: 1.80; 95% CI: 1.32, 2.46 and MUACAZ OR: 1.42; 95% CI: 1.10, 1.84) (**Table 3**). All associations detected in unadjusted analysis remained after adjustment for age, sex, and SES factors (Adjusted Model 1, Table 3). Furthermore, ORs remained approximately the same after controlling for preschool ear infections with discharge (Adjusted Model 2, Table 3).

Risk of hearing loss and abnormal tympanometry in young adulthood by preschool nutrition status

The risk of having both hearing loss and abnormal tympanometry by early childhood anthropometric status is summarized in **Table 4**. Hearing loss and abnormal tympanometry were associated with stunting (HAZ OR: 2.19; 95% CI: 1.30, 3.72), underweight (WAZ OR: 1.87; 95% CI: 1.19, 2.92), and wasting (BMIAZ OR: 2.24; 95% CI: 1.32, 3.79; MUACAZ OR: 2.15; 95% CI: 1.37, 3.40) in the unadjusted models. ORs remained comparable or stronger after controlling for SES factors and for preschool ear infections with discharge (Adjusted Models 1 and 2, Table 4).

Preschool vitamin A receipt

Four-monthly vitamin A compared with placebo receipt, as randomly assigned during the original trial, was introduced as an interaction term with each nutritional indicator in each outcome model and was found to be not significant (data not shown).

TABLE 2
Risk of hearing loss in young adulthood by preschool nutritional status ($n = 2193$), Sarlahi, Nepal 2006–2008[1]

Status indicators	Subjects, *n*	Hearing Loss			Adjusted Model 1[3] OR (95% CI)	Adjusted Model 2[4] OR (95% CI)	Adjusted Model 3[5] OR (95% CI)	Adjusted Model 4[6] OR (95% CI)
		n	%	OR[2] (95% CI)				
HAZ								
≥−2	791	34	4.3	—	—	—	—	—
<−2	1402	96	6.9	1.64 (1.10, 1.45)	1.78 (1.17, 2.71)	1.77 (1.15, 2.74)	1.80 (1.13, 2.86)	1.77 (1.16, 2.70)
WAZ								
≥−2	1112	50	4.5	—	—	—	—	—
<−2	1081	80	7.4	1.70 (1.18, 2.44)	1.75 (1.21, 2.52)	1.76 (1.20, 2.58)	1.42 (0.95, 2.12)	1.75 (1.21, 2.53)
BMIAZ								
≥−2	1936	105	5.4	—	—	—	—	—
<−2	257	25	9.7	1.88 (1.19, 2.97)	1.94 (1.20, 3.15)	1.99 (1.20, 3.30)	1.33 (0.77, 2.30)	1.97 (1.22, 3.20)
MUACAZ								
≥−2	1596	76	4.8	—	—	—	—	—
<−2	496	48	9.7	2.14 (1.47, 3.12)	2.19 (1.50, 3.21)	2.23 (1.49, 3.33)	1.78 (1.16, 2.73)	2.22 (1.52, 3.26)

[1]Hearing loss is defined by pure-tone average >30 dB (0.5, 1, 2 and 4 kHz) in the worse hearing ear. Nutritional status *z* scores were calculated with the use of the WHO Multicenter Growth Reference Study child growth standards (http://www.who.int/childgrowth/en/). BMIAZ scores were missing for 5 subjects and MUACAZ scores were missing for 100 subjects. A further 7 observations were dropped from each adjusted model due to missing SES information. BMIAZ, BMI-for-age *z* score; HAZ, height-for-age *z* score; MUACAZ, mid-upper arm circumference–for-age *z* score; WAZ, weight-for-age *z* score.

[2]ORs were calculated by exponentiating the β-coefficient of logistic regression; 95% CIs were calculated by exponentiating the values ($+1.96 \times$ standard error of the β-coefficient).

[3]Adjusted Model 1: OR adjusted for age at baseline (<12 mo vs. ≥12 mo), sex (male vs. female), head of household literacy (yes vs. no), occupation [private, business, or government service (referent), farmer or laborer], caste (higher vs. lower or other), living rooms in house (one vs. more than one) and water source (ring well or other vs. tube well).

[4]Adjusted Model 2: OR adjusted for same variables as Model 1, plus ≥3 episodes of ear infection with discharge during the original trial.

[5]Adjusted Model 3: OR adjusted for same variables as Model 1, plus abnormal tympanometry during follow-up trial.

[6]Adjusted Model 4: OR adjusted for same variables as Model 1, plus cerumen impaction during follow-up trial.

DISCUSSION

To our knowledge, this is the largest population-based study with the longest follow-up period conducted in a developing country to document poor nutritional status during preschool years as a risk factor for hearing loss in adult life. Hearing loss has been associated with malnutrition in other settings, including prisoners of war (33–35) and periods of acute food deprivation in civilians (36, 37). In these scenarios, the observed hearing loss is sensorineural and is often accompanied by neuropathies and vision problems. The severity of hearing loss has ranged from mild to profound and has been noted to persist beyond resolution of other symptoms. Theories on the underlying pathophysiology include demyelination of the 8th cranial nerve (34) and metabolic lesions such as mitochondrial damage that selectively affect neurons with high energy consumption (36). Studies of protein malnutrition in rats support the vulnerability of the auditory brainstem pathway to nutritional insults (22, 23).

In our study, anthropometric indicators of early childhood wasting and stunting were consistently associated with a 1.8- to 2.2-fold higher risk of early-adult hearing loss. An important distinction emerged in the risk associated with tympanometric findings to suggest potentially distinct pathways underlying these associations. Acute undernutrition in early childhood, represented by a low BMI or thin arm circumference for age, was associated with both an ~2-fold higher risk of hearing loss and a 1.4- to 1.8-fold increased risk of abnormal tympanometry. When controlling for abnormal tympanometry, the relation between hearing loss and indicators of acute undernutrition were weakened. This is an expected reduction in the risk relation given the coexistence between infection and acute or wasting malnutrition. A similar pattern is observed with weight-for-age, a composite indicator that is highly influenced by BMI. Stunting, by contrast, was associated with a 1.6-fold increased risk of hearing loss in young adulthood that remained when controlling for abnormal tympanometry. When considering the risk of hearing loss and abnormal tympanometry in combination, however, the relative odds of hearing loss in children with early childhood stunting was increased to 2.2, suggesting that infections were likely to have been at least partially involved in the pathophysiology of hearing loss associated with both wasting and stunting (38, 39). Several observational studies have similarly noted that children who are underweight or acutely malnourished are at higher risk for otitis media (40, 41). The susceptibility to infectious disease among malnourished children is presumed to be related to decreased immune system function (42, 43), although animal studies of middle-ear mucosa have not been conducted to confirm this relation specific to middle-ear pathology.

Aside from the increased risk of hearing loss with abnormal tympanometry, chronic undernutrition, indicated by stunting, was also associated with later-life hearing loss with normal middle-ear function. This association with sensorineural hearing loss suggests involvement of an alternative mechanism in addition to the infectious pathway. Early childhood stunting reflects not only poor postnatal nutrition and morbidity, but also in utero nutritional exposures and impaired growth (44). Christian et al. (45) recently evaluated the relation between small-for-gestational age and stunting in early childhood using 19 longitudinal birth cohorts worldwide that included >44,000 children. Small-for-gestational age at birth was associated with a 2.4–4.5 times increased odds of early childhood stunting, with a

TABLE 3
Risk of abnormal tympanometry in young adulthood by preschool nutrition status ($n = 2174$), Sarlahi, Nepal, 2006–2008[1]

Status indicators	Subjects, *n*	Abnormal tympanometry			Adjusted Model 1[3]	Adjusted Model 2[4]
		n	%	OR[2] (95% CI)	OR (95% CI)	OR (95% CI)
HAZ						
≥−2	785	119	15.2	—	—	—
<−2	1389	241	17.4	1.18 (0.93, 1.49)	1.19 (0.92, 1.52)	1.16 (0.89, 1.51)
WAZ						
≥−2	1101	154	14.0	—	—	—
<−2	1073	206	19.2	1.46 (1.16, 1.84)	1.46 (1.16, 1.84)	1.48 (1.16, 1.89)
BMIAZ						
≥−2	1920	297	15.5	—	—	—
<−2	254	63	24.8	1.86 (1.32, 2.46)	1.91 (1.38, 2.65)	2.02 (1.43, 2.84)
MUACAZ						
≥−2	1585	241	15.2	—	—	—
<−2	488	99	20.3	1.42 (1.10, 1.84)	1.42 (1.09, 1.84)	1.42 (1.08, 1.88)

[1]Abnormal tympanometry is defined as an abnormal height peak height (<0.3 or >1.4 mmho) or width (<50 or >110 daPa). Nutritional status *z* scores were calculated with the use of the WHO Multicenter Growth Reference Study child growth standards (http://www.who.int/childgrowth/en/). BMIAZ scores were missing for 5 subjects, and MUACAZ scores were missing for 101 subjects. Seven further observations were deleted from each adjusted models due to missing SES information. BMIAZ, BMI-for-age *z* score; HAZ, height-for-age *z* score; MUACAZ, mid-upper arm circumference–for-age *z* score; WAZ, weight-for-age *z* score.

[2]ORs were calculated by exponentiating the β-coefficient of logistic regression; 95% CIs were calculated by exponentiating the values ($+1.96 \times$ standard error of the β-coefficient).

[3]Adjusted Model 1: OR adjusted for age at baseline (<12 mo vs. ≥ 12 mo), sex (male vs. female), head of household literacy (yes vs. no), occupation [private, business or government service (referent), farmer or labourer], caste (higher vs. lower or other), living rooms in house (one vs. more than one), and water source (ring well or other vs. tube well).

[4]Adjusted Model 2: OR adjusted for same variables as Model 1, plus ≥3 episodes of ear infection with discharge during the original trial.

population-attributable risk of 20%. Thus, our young adult subjects who were stunted as preschoolers likely experienced substantial fetal growth restriction. Therefore, it is plausible that the observed associations between early childhood nutritional status and hearing loss reflect, in part, a consequence of in utero nutritional exposures, suggesting an etiologically relevant period for hearing loss in association with malnutrition that extends from fetal life through the preschool years.

Given that periodic preschool vitamin A receipt reduced hearing loss associated with early childhood otitis media (46), we tested and found no evidence of interaction between vitamin A receipt in the original trial and relative odds of hearing loss or abnormal tympanometry associated with wasting or stunting. This suggests that the risk of hearing loss posed by protein-energy malnutrition was independent of protective effects of vitamin A against otitis media-related hearing loss during the preschool years.

A limitation to this study is the substantial number (45%) of subjects eligible for follow-up at the end of the preschool trial who were not assessed for hearing ability in young adulthood. Those young adults whom we did not measure were more likely to be women, older in age, and of lower SES. However, bias is unlikely to threaten the validity of our findings because the early childhood demographic and socioeconomic factors that differed between the 2 assessment groups were not related to hearing loss in young adulthood.

We did not collect information on history of hearing loss at birth, speech-language delay, cleft lip or palate, or noise exposure in the original trial. These factors would have been helpful in eliciting timing and etiology of hearing loss in our cohort and represent limitations in the study design. There are known infectious etiologies of perinatal sensorineural hearing loss, such as congenital cytomegalovirus (CMV) infection, which were not considered within this study (47). While CMV-associated hearing loss has been well studied in the United States and Europe, there are no data published to date on prevalence of CMV-associated hearing loss in Nepal (48, 49). Considering the emerging evidence on geographic and socioeconomic disparities of CMV infection, evaluation of CMV-related hearing loss in low-resource settings, and its relation with undernutrition, are areas that warrant future study (50, 51).

This study was conducted in a rural, chronically undernourished South Asian population with limited access to healthcare services, representing the type of population to which these findings may be most relevant. However, the extent to which these findings reported here reflect conditions in better-nourished, healthier populations remains unknown. Caution should be used when generalizing these findings to populations with better access to healthcare.

This is the first study to our knowledge to identify early childhood nutritional status as a modifiable risk factor for later-life hearing loss. Children whose anthropometric status lies below conventional cutoffs for undernutrition may face an increased lifelong risk of hearing loss and middle-ear disease and could benefit from periodic ear examinations early in life. Further evaluation of the mechanisms underlying these associations is urgently needed.

TABLE 4
Risk of hearing loss and abnormal tympanometry in young adulthood by preschool nutrition status ($n = 2174$), Sarlahi, Nepal, 2006–2008[1]

Status indicators	Subjects, *n*	Hearing loss and abnormal tympanometry			Adjusted Model 1[3]	Adjusted Model 2[4]
		n	%	OR[2] (95% CI)	OR (95% CI)	OR (95% CI)
HAZ						
≥−2	785	18	2.3	—	—	—
<−2	1389	68	4.9	2.19 (1.30, 3.72)	2.36 (1.36, 4.08)	2.41 (1.35, 4.30)
WAZ						
≥−2	1101	31	2.8	—	—	—
<−2	1073	55	5.1	1.87 (1.19, 2.92)	1.89 (1.20, 2.97)	1.94 (1.20, 3.15)
BMIAZ						
≥−2	1920	67	3.5	—	—	—
<−2	254	19	7.5	2.24 (1.32, 3.79)	2.30 (1.32, 4.02)	2.54 (1.39, 4.66)
MUACAZ						
≥−2	1585	50	3.2	—	—	—
<−2	488	32	6.6	2.15 (1.37, 3.40)	2.20 (1.38, 3.48)	2.27 (1.37, 3.74)

[1]Hearing loss is defined by pure-tone average >30 dB (0.5, 1, 2 and 4 kHz) in the worse hearing ear. Abnormal tympanometry is defined as an abnormal height peak height (<0.3 or >1.4 mmho) or width (<50 or >110 daPa). Nutritional status *z* scores were calculated with the use of the WHO Multicenter Growth Reference Study child growth standards (http://www.who.int/childgrowth/en/). BMIAZ scores were missing for 5 subjects and MUACAZ scores were missing for 101 subjects. Seven further observations were deleted from each adjusted models due to missing SES information. BMIAZ, BMI-for-age *z* score; HAZ, height-for-age *z* score; MUACAZ, mid-upper arm circumference–for-age *z* score; WAZ, weight-for-age *z* score.

[2]ORs were calculated by exponentiating the β-coefficient of logistic regression; 95% CIs were calculated by exponentiating the values ($+1.96 \times$ standard error of the β-coefficient).

[3]Adjusted Model 1: OR adjusted for age at baseline (<12 mo vs. ≥ 12 mo), sex (male vs. female), head of household literacy (yes vs. no), occupation [private, business or government service (referent), farmer or laborer], caste (higher vs. lower or other), living rooms in house (one vs. more than one) and water source (ring well or other vs. tube well).

[4]Adjusted Model 2: OR adjusted for same variables as Model 1, plus ≥3 episodes of ear infection with discharge during the original trial.

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