BMJ

BMJ 2012;344:d7962 doi: 10.1136/bmj.d7962 (Published 10 January 2012)

RESEARCH

Vitamin A supplementation in preschool children and risk of hearing loss as adolescents and young adults in rural Nepal: randomised trial cohort follow-up study

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Abstract

Objective To determine whether vitamin A supplementation administered in the preschool years can lower the risk of hearing loss in adolescence and adulthood.

Design Follow-up study of adolescents and young adults who, as preschool aged children in 1989, were enrolled into a cluster randomised, double blinded, placebo controlled trial of vitamin A supplementation.

Setting South central, rural Nepal.

Participants 2378 adolescents and young adults aged 14 to 23, representing 51% of those who finished the original trial and 71% of those living in the study area in 2006.

Interventions Every four months for 16 months preschool children were visited at home, given an oral 200 000 IU dose of vitamin A (half dose at age 1-11 months, quarter dose at <1 month) or placebo and the parents were queried about any childhood illnesses in the previous week, including purulent discharge from the ears.

Main outcome measures Prevalence of mild or worse hearing loss (≥30 dB) in the most affected ear and tympanometric measures of middle ear function (peak height, ear canal volume, and gradient).

Results During the original trial, the prevalence of middle ear infection during the preschool years did not differ between the supplement groups. By adolescence and early adulthood, a non-significant 17% reduction in hearing loss occurred among those who had periodically received vitamin A compared with placebo as preschool aged children (odds ratio 0.83, 95% confidence interval 0.62 to 1.12). Among participants with any ear discharge in early childhood, vitamin A supplementation was associated with a reduced risk of hearing loss, by 42% (0.58, 0.37 to 0.92) compared with controls, after adjusting the confidence interval for the design effect of the original trial. Abnormal tympanometric peak height of the middle ear system was less likely among participants supplemented with vitamin A in childhood.

Conclusion In undernourished settings, periodic, high dose vitamin A supplementation may reduce the risk of hearing loss associated with purulent ear infections in early childhood.

Introduction

Hearing loss severe enough to disrupt communication and socialisation affects an estimated 278 million people worldwide, two thirds of whom live in the developing world.[1 2] Hearing disability limits economic and educational opportunities,[3 4] especially in low income countries where rehabilitation services are lacking.[2 4] Most hearing loss among children living in poverty is attributable to chronic otitis media.[2]

There is limited epidemiological evidence that deficiencies in certain nutrients, such as iron, zinc, copper, calcium, and vitamins A and D, may increase susceptibility to ear infections,[5] and that supplementation with micronutrients in undernourished settings may attenuate the risk of otitis media in children. For example, two supplementation trials among preschool aged children, in Bangladesh[6] and Kenya,[7] reported reductions in otitis media after routine supplementation with zinc and vitamin A, respectively. Both nutrients regulate numerous metabolic pathways involved in host defence mechanisms,[5] which when compromised could increase the frequency, duration, or severity of ear infections that, in turn, could increase the risk of hearing

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loss. No trials to our knowledge have followed participants to assess the effect of nutritional supplementation on hearing loss.

Southern Asia is a relevant region in which to explore the causal association and public health impact of vitamin A deficiency on hearing loss, as both conditions coexist and are widely prevalent. The prevalence of vitamin A deficiency in southern Asia is about 33%, and approximately 45% of vitamin A deficient preschool children in the world reside in the region.[8] The World Health Organization estimates that chronic otitis media affects between 1.4% and 7.8% of children in South East Asia.[9] Within Nepal, vitamin A deficiency affects an estimated 32% of preschool children,[10] and 8% of children aged 5 to 15 years have a diagnosis of hearing loss.[11] Abnormal tympanometry in either ear, often attributable to current or past otitis media, has been estimated to affect 25% of young people in the country.[12]

In the present study, in Nepal, we examined the causal effect of randomised, periodic receipt of high dose (200 000 IU) vitamin A during the preschool years on hearing loss in early adulthood. We hypothesised that discharge from the ears, prospectively monitored during early childhood, would be positively associated with hearing loss, and that vitamin A supplementation during that early period would lower this risk by attenuating the frequency, duration, or severity of middle ear infection compared with a group randomised to placebo in early childhood.

Methods

We carried out a study of ear health and hearing among a cohort of adolescents and young adults aged 14 to 23 and living in the Sarlahi district of south central Nepal. In their preschool years these participants had taken part in a double blinded, placebo controlled cluster randomised trial of vitamin A supplementation (NNIPS-1, the first trial of the Nepal Nutrition Intervention Project-Sarlahi) between 1989 and 1991.[13]

Original trial

During the original trial, 261 administrative wards in the 29 contiguous village development communities in Sarlahi were randomised, blocked on contiguous village development communities. Preschool children were to receive a vitamin A supplement (200 000 IU for children aged 12 months or older, 100 000 IU for 1 to 11 months, and 50 000 IU for <1 month) or an identical placebo capsule (containing 1000 IU vitamin A) during home visits every four months.

During a baseline visit (September to December 1989), children aged 60 months or younger were enumerated, dosed with supplements assigned by ward, measured for mid-upper arm circumference to reflect nutritional status, and evaluated for morbidity by parental interview about the number of days in the past week in which the child was reported to have had fever, cough, loose watery or bloody stools, or discharge of pus from either ear (an indicator of middle ear infection). To improve reliability, morbidity histories were recorded only if children had been with their parent or guardian for the previous seven days, a condition met by about 90% of respondents at each visit.

Supplementation and anthropometric and morbidity assessments were repeated during home visits every four months, during which new infants were also recruited into the trial. Household socioeconomic and demographic information was recorded at the time of the second of the four-monthly visits. Although originally planned for two years, the trial was stopped after 16 months for children aged 6 months or older after a data and safety monitoring analysis showed a highly significant 30% reduction in mortality attributed to vitamin A.[13] Thereafter, children aged 6 months or older received a high dose of vitamin A, whereas infants enrolled for a subsequent year remained in the trial up to 6 months of age.

Trial substudy cohort

A subset of 40 (15%) of the 261 enlisted wards, 20 per supplement group, was randomly selected for enrolled children to receive additional nutritional and health assessments at central sites, including an otoscopic examination of the ear by a doctor at the first and fifth visits. The examination, carried out blinded to the findings by parental history, enabled the history of ear discharge to be validated against clinical appearance recorded on the same day, which showed excellent agreement (κ=0.75).[14]

Participants in the present study were members of the baseline cohort of preschool children aged less than 5 at enrolment, who had been maximally exposed to the nutrient supplement protocol (five 200 000 IU of vitamin A *v* placebo) and the risk of acquiring a detectable, preschool ear infection during the period of the trial (five examinations over a 16 month period). To maximise our ability to accurately classify the status of ear discharge during the trial, we excluded participants with 60% or more incomplete data on ear discharge—that is, children with three, four, or all five of their reports on ear discharge missing.

Follow-up study

Participants known to have survived to the end of all data collection activities related to the trial in 1992 were listed by the Nepal Nutrition Intervention Project-Sarlahi project's data management centre. This list enabled confirmation of the identity and residential and vital status of participants at the outset of a health and nutrition assessment of the cohort in 2006-8. At an initial follow-up home visit, original trial staff, who remained continuously employed by the project during the interim, obtained informed consent and updated data on individual vital status, residency, marriage, schooling, occupation, and (for females) pregnancy status, as well as household socioeconomic status. From these home visits, we identified potential contacts who provided the list of cohort members sought for follow-up assessment.

After ascertainment of vital status, we carried out an assessment of ear health and hearing by previously described methods at a convenient central site in each ward.[12] Technicians, blinded to the original supplement allocation of the ward, carried out the ear examinations and hearing assessments. Ear wax was not removed before the examination. Technicians examined the external ear, tympanic membrane, and middle ear using a lighted otoscope (mini 2000 otoscope; Heine, Herrsching, Germany). Ear health and function were measured through tympanometric measurements taken at varied air pressure levels using a portable tympanometer (Micro Tymp 2; Welch-Allyn, Skaneateles Falls, NY), which varied the pressure in the ear canal from 200 to −400 decapascals (daPa), providing data on admittance of the middle ear system (peak height and gradient) and ear canal volume at 200 daPa. Audiometry was carried out using a digital audiometer (240 digital audiometer; Amplivox, Oxford, UK) and foam tipped insert earphones (Auditory System; E-A-R, Indianapolis, IN). Participants were considered to have failed hearing screening if they did not respond to a 30 decibel (dB) tone in either ear at any of the frequencies of 0.5, 1, 2, 4, and 8 kilohertz (kHz).[12] Participants who failed the screening were tested to establish air conduction thresholds at 0.5, 1, 2, 4, and 8 kHz in both ears.

We used a two staged measure of hearing disability as the primary outcome: screening failure and hearing loss, defined as a mean of threshold values for air conduction at 0.5, 1, 2, and 4 kHz greater than or equal to 30 dB in the worst affected ear among those who failed screening.[12] This definition represents a deficit in hearing at the middle frequencies that is commonly used in audiology and is widely associated with difficulties in communication.[15-17]

Statistical analysis

We used the χ^2 test to compare supplementation groups on personal and household factors measured at the baseline visit of the original trial and at the follow-up study 17 years later. Differences in risk of failing screening and exhibiting hearing loss in adolescents and young adults in the supplementation groups were estimated by the odds ratio and absolute risk difference. Since supplementation was originally allocated by cluster (ward), we adjusted 95% confidence intervals using generalised estimating equations regression models,[18] specified as binomial with an identity and logit link for absolute risk difference and odds ratio estimates,[19] respectively, and exchangeable correlation structure.

Because of the potential for imbalance between groups associated with losses to follow-up in the intervening years and non-response among re-contacted participants, we also adjusted odds ratios and absolute risk differences for several covariates using sequential multivariable logistic regression analyses.[20] Age and sex were included in the full models. We considered variables as potential confounders and included them in the model if associated (P<0.10) with either supplementation group allocation or hearing status. All analyses were done using STATA, version 10.0, software.

Results

In total, 4765 children from newborn to 60 months of age were recruited into the baseline cohort substudy area of the original trial; 2507 (52.6%) were allocated by ward to receive vitamin A and 2258 (47.4%) to receive placebo (fig 1⇓). Forty three and 52 children, respectively, died between the baseline (first) and fifth visits of the original trial. During the next 16 years, 172 children died (100 in vitamin A group and 72 in placebo group) and 1138 (622 and 516, respectively) had moved from the study area, leaving 71% (1742 in vitamin A group) and 73% (1618 in placebo group) of the original cohorts as potential participants. Of these, 86% and 83% of participants in each group were contacted and 75% (1304 in vitamin A group) and 72% (1165 in placebo group) examined and tested for hearing in 2006-8.

Respondents in both supplementation groups were comparable on a wide range of household socioeconomic (table 1⇓) and personal (table 2⇓) characteristics, as assessed during the original trial and the follow-up study. No systematic patterns were apparent among the few differences observed between participants of each original supplement group who were followed-up. Slightly fewer heads of households reported completing secondary education and having farming as their occupation in the vitamin A group than placebo group, with the occupational difference persisting among the adolescents and young adults at follow-up. Fewer females were tested at follow-up in both groups, reflecting a pattern of young women marrying and leaving home earlier in life than young men.[21] During the five four-monthly visits of the trial, about 19% of participants reported at least one episode of discharging pus in either ear during the previous week; about 45% of these reported two or more positive episodes. Around 72% of reports on ear discharge were for seven or more days, and 38% to 52% of cases during any given visit reported having discharge on the next visit (data not shown), seeming to reflect the chronicity of purulent episodes. Vitamin A supplementation seemed to have no effect on the prevalence of weekly ear discharge during the trial (table 2).

At follow-up, the prevalence of screening failure and hearing loss among participants was 11.7% (278/2373) (95% confidence interval 10.4% to 13.0%; table 3⇓) and 5.9% (140/2370) (5.0% to 6.9%; table 4⇓), respectively. Risk of hearing loss was associated with reported episodes of ear discharge in a dose-response relation, with the odds ratio increasing from 2 to 17 as the number of reported childhood weekly episodes of ear discharge (one or more days with symptoms in the previous week) increased, compared with those reporting no episodes (fig 2⇓). All odds ratios and 95% confidence intervals, adjusted for original design effect, excluded 1.0. Virtually the same pattern was observed for screening failure (data not shown).

Tables 3 and 4 present the findings on effects of preschool vitamin A supplementation on risks of failing screening and hearing loss, respectively. Compared with placebo, receipt of vitamin A had no overall effect on the risk of failing screening (odds ratio 0.97, 95% confidence interval 0.69 to 1.35; absolute risk difference −0.3%, 95% confidence interval −3.9% to 3.2%), but seemed to reduce the risk of hearing loss, by 17% (0.83, 0.62 to 1.12; −1.0%, −2.7% to 0.7%). Among participants without reported ear discharge over any of the five four-monthly weekly reports, preschool vitamin A supplementation had no effect on the risk either of failing screening (1.17, 0.78 to 1.76; 1.2%, −1.9% to 4.2%) or hearing loss (1.07, 0.64 to 1.80; 0.2%, −1.5% to 1.9%). Among children with any preschool ear discharge (one in five times or more), the odds ratio and absolute risk difference estimates were 0.71 (0.44 to 1.14) and −6.8% (−16.4% to 2.7%) for failure of hearing screening, and 0.58 (0.37 to 0.92) and −7.2% (−13.0% to −1.4%) for hearing loss, respectively. Multivariable analysis (adjusting for design, sex, age at enrolment into the original trial, caste, and head of household occupation), resulted in virtually identical odds ratios of 0.69 (0.42 to 1.13) for failure of hearing screening and 0.58 (0.38 to 0.89) for hearing loss among participants with a history of ear discharge and allocated to receive preschool vitamin A compared with placebo in early childhood.(data not shown).

We assessed the impact of vitamin A on hearing loss for two aspects of severity, one related to ear discharge and the other to extent of hearing loss. There was no evidence of increased protection against ear discharge by vitamin A on hearing loss by the number of ear discharge reports in early childhood: the odds ratio for screening failure and hearing loss in vitamin A compared with placebo recipients for one reported episode was 0.44 (95% confidence interval 0.19 to 1.04) and 0.28 (0.09 to 0.85) and for two to five episodes was 0.79 (0.44 to 1.42) and 0.76 (0.44 to 1.33), respectively. We tested the extent of hearing loss by applying a more stringent threshold of greater than 40 dB for defining hearing loss in the worst affected ear. Against this cut-off, the protective odds ratio against hearing loss was stronger, 0.42 (0.21 to 0.82), although the absolute rates, 5.0% (12/242) and 10.8% (23/214) and absolute risk difference (−5.9%, 95% confidence interval −9.9% to −2.2%) did not widen (data not shown).

Tympanometry revealed a lower odds ratio of having an abnormal tympanic membrane peak height associated with previous receipt of vitamin A (odds ratio 0.83, 95% confidence interval 0.67 to 1.03), with estimates close to one for gradient (odds ratio 0.97) and volume (0.95; table 5⇓). Stratification revealed similar estimates for odds ratios in participants without

and with preschool ear discharge for peak height and gradient, although odds ratios related to volume varied qualitatively. All 95% confidence intervals included 1.0.

Discussion

In this chronically undernourished rural South Asian setting, periodic, high dose vitamin A supplementation in early childhood significantly reduced the relative odds of hearing loss associated with early childhood middle ear infection by 42%. This effect translated into a significant 7% absolute reduction in hearing loss, from 20%, among those known to have had early childhood ear discharge, and about a 1% absolute (17% relative) decline, from 6.5% to 5.4%, in hearing loss from all causes. Although suggestive from the literature over the past 80 years,[5 22 23] to our knowledge this is the first study to show protection conferred by vitamin A against hearing loss of likely infectious origin.

Context of vitamin A effect

This latent effect of vitamin A supplementation was observed in a vitamin A deficient rural setting. At the outset of the trial, around 1990, the prevalence of xerophthalmia was about 3.5%,[24] reflecting ocular manifestations of vitamin A deficiency, later affirmed by a national survey reporting 33% of preschool children in the subtropical plains of southern Nepal to have hyporetinolaemia[10] (serum retinol concentration below the conventional cut-off for deficiency of 0.70 µmol/L; referent median, 5th-95th percentiles for 4-8 years: 1.20, 0.84 to 1.58 µmol/L).[25] Both estimates classify this population as vitamin A deficient.[26] The public health burden of vitamin A deficiency was further shown by the 30% reduction in mortality among children who received vitamin A in the original trial.[13] Purulent ear infection was a common childhood condition, as reported by a clinically validated parental history,[14] affecting 20% of participants in the population cohort, half of whom reported having had a discharging ear on at least two occasions (table 2). Although the two groups did not differ in weekly prevalence of ear discharge, child mortality after an acute episode (discharge for <7 days but not longer) was noticeably reduced with vitamin A supplementation, evident by a protective odds of 0.24 (95% confidence interval 0.07 to 0.80) compared with recipients of placebo (K P West Jr et al, unpublished data, 2011).

The effect of vitamin A was observed in a population where, in 2006-8, hearing loss in either ear affected 6.5% of adolescents and young adults—that is, those who had received placebo during the original trial. This frequency is comparable to a prevalence of 8.3% reported from a hearing survey carried out in the terai in the mid-90s among children aged 5-15 years,[11] before the launch of the country's national vitamin A programme. Against this stable prevalence, the observed 42% reduction in hearing loss due to ear discharge in the vitamin A recipient group provides a basis for the 17% overall reduction to be interpreted as the fraction of mild or worse hearing loss that should be preventable by a programme for vitamin A supplementation in preschool children.

Biological plausibility

The protective effect of vitamin A we observed is posited to have occurred through a reduction in the severity of middle ear infection by host defence mechanisms, regulated by vitamin A,[27-29] that are involved in maintaining epithelial integrity, modulating oxidative stress, and regulating the immune response, thereby controlling inflammatory processes that may damage the ear and impair hearing. Possibly central to each mechanism is the regulatory influence of vitamin A on cell proliferation, differentiation, and apoptosis, as exerted through its nuclear receptors on gene expression and protein synthesis.[30] Experimental vitamin A deficiency leads to a loss in integrity of normally ciliated, mucus secreting epithelium in the middle ear, a degradative process characterised by keratinising metaplasia, oedema, and inflammation.[31-33] Other pathological changes may include a degeneration of auditory nerves and cochlea and overgrowth of ossicular bone.[33] However, treating experimental otitis media or sinusitis with vitamin A in animals has been shown to reduce mucosal disruption, enhance antioxidant enzyme activity (for example, superoxide dismutase and glutathione peroxidase), and lower free radical production (for example, lower concentrations of malondialdehyde and nitric oxide).[34-36] Vitamin A modulates innate and adaptive immune responses to infection,[29] favouring Th2-type, T regulatory, and apoptotic pathways that may be expected to control inflammation, oxidative stress, and consequent tissue destruction[37] and that may reduce the risk of long term suppurative, ossicular, and tympanic damage.[5] Studies in nutritionally vulnerable populations have reported that children with acute otitis media have disturbed antioxidant enzyme activity and tend to have low antioxidant nutrient status,[38-40] including vitamin A deficiency,[22 39 41 42] conditions that may favour an inappropriate or less controlled inflammatory response to middle ear infection. One trial, among Kenyan children admitted to hospital for measles, observed a 74% decline (95% confidence interval 8% to 95%) in incident otitis media among participants randomised to large dose vitamin A compared with placebo on admission,[7] but the children were not followed for hearing loss.

Clinical coherence

We evaluated the consistency of the protective effect of vitamin A against hearing loss for tympanometric findings and response-gradient thresholds. Hearing loss in this population was accompanied by ear drum dysfunction, as measured by abnormal membrane peak height, gradient, or volume.[12] However, only in peak height was improved function in participants supplemented with vitamin A compared with placebo suggested, irrespective of ear discharge in early childhood. Although unexpected, comparable tympanic function may still be compatible with improved hearing among vitamin A supplemented cases, given that membrane lesions resulting from otitis media in early life may recover,[43] and, aside from conductive loss related to disturbance of the ear drum, middle ear infection may also induce sensorineural hearing loss by disturbing cochlear function,[44] hair cell loss, and other diseases within the inner and middle ear,[45] not observed with tympanometry. Finally, with a quarter of participants having abnormal tympanometry,[12] further injurious exposures under harsh, rural conditions in the interim years could have negated potential tympanic differences between groups.

We also assessed the protective response of vitamin A for apparent severity of hearing loss in adolescents and young adults and ear discharge in early childhood. There was a stronger, protective relative odds of vitamin A against hearing loss when the tone threshold was increased from 30 dB (odds ratio 0.58) to a more stringent cut-off of more than 40 dB (0.42). The finding is consistent with stronger protective risks ascribed to vitamin A in other trials by using more stringent definitions of infections such as diarrhoea, measured as number of stools daily,[46 47] or severity of general illness based on level of care sought.[47] However, although the risk of hearing loss increased with the frequency of ear discharge during the original trial (fig

2), we failed to observe a parallel gradient in protection with vitamin A. One explanation may be that the therapeutic action of vitamin A occurs during the early, acute inflammatory phase rather than the chronic or recurrent periods of purulent ear infection. Alternatively, the lack of a dose-response effect could have occurred by chance given the breadth of confidence intervals around the odds ratios related to one or more than one week of reported ear discharge.

Completeness of follow-up

An a priori hypothesis was tested in this study that was established during the original trial's design, based on earlier reports of an association between vitamin A deficiency and otitis media.[22 23 42] In a cohort randomised to an exposure in early life, high rates of follow-up permit an inference about cause and effect to be drawn.[48] In each group, we evaluated hearing in about 51% of participants believed to have survived the 16 interim years since the end of the trial and in 71% of participants considered potentially contactable in the study area. About 15% of those considered as potential participants could not be found with repeated visits, suggesting emigration from the area. Despite losses to follow-up, internal validity possibly protected on the basis of comparability in the proportionate losses from each group and the similarity of assessed individuals in each group on numerous characteristics evaluated during the original trial and at the time of follow-up. With respect to external validity, although participants assessed as adolescents and young adults in both groups differed in several ways from those not followed, it does not seem that factors for which imbalances were observed (sex, socioeconomic status, and age) were, in this population, associated with either a history of purulent ear infection or current hearing, suggesting low probabilities of bias associated with losses to follow-up.

Strengths and limitations of the study

Carrying out hearing assessments in open, rural community settings, rather than in a sound proofed clinic, challenges the control of ambient sound and accuracy of testing. However, we believe the integrity of our testing protocol was enhanced by using insert earphones, an accessory that attenuates ambient noise, and pausing or restarting hearing tests that were disturbed by obvious sounds. To facilitate monitoring of the ambient noise levels we used a sound level meter. Supplements during the initial double blinded, randomised trial were taken with high compliance (>90%) in both the vitamin A and placebo groups, providing assurance of intended nutritional exposure. Multiple, prospective assessments of ear discharge over a consecutive 16 month period enabled the occurrence of ear discharge to be monitored for a substantial period of early childhood. Measurement bias was minimised by assuring that field technicians doing the hearing tests and examinations were blinded to the original supplementation assignment of each community.

Conclusions and policy implications

In this rural Nepalese population, periodic, high dose vitamin A supplementation in early childhood was associated with a reduction in the risk of hearing loss from middle ear infection in adolescence and young adulthood. Levels of detected hearing loss were mild or worse in the most affected ear, and sufficiently severe to disrupt normal activities of daily living and socialisation.[12] To the degrees that risks of ear infection, vitamin A deficiency, and hearing impairment observed in the terai of Nepal coexist elsewhere in rural South Asia, current, ongoing programmes for vitamin A supplementation in preschool children designed and intended to prevent xerophthalmia[49] and child mortality[13] may be substantially attenuating risks of hearing loss in the region, providing an additional public health indication for vitamin A prophylaxis in early childhood in areas of high deficiency.

We thank Christine Stewart, Parul Christian, James Tielsch, Luke Mullany, Sharada Ram Shrestha (deceased), Darrell Mast, Andre Hackman, and Tirta Raj Sakya; field and data management staff of the study team; and hearing technicians, Jaisi Lal (deceased) and Matrika Dungel.

Contributors: JS designed the follow-up hearing study, supervised training and data collection, conducted data analysis and interpretation, and wrote the first draft of the manuscript. KPW (principal investigator of original trial and the larger cohort follow-up study) conceived and assisted in the design of the hearing study and edited the manuscript. LW contributed to data analysis and interpretation and edited the manuscript. SLC and SKK developed study procedures and supervised implementation of the original trial, larger follow-up study, and hearing study. SLK trained and provided continuing technical oversight of the hearing technicians and helped develop the hearing assessment protocol. JK assisted in the analysis and interpretation of the data and edited the manuscript. JP helped develop ear health and audiometry assessments, assisted in the interpretation of audiometric and ear health data, and edited the manuscript. All authors had full access to all of the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. KPW is the guarantor.

Funding: This follow-up study was supported by grant No GH614 (Control of Global Micronutrient Deficiency) between the Bill and Melinda Gates Foundation, Seattle, and the Center for Human Nutrition, Department of International Health of the Johns Hopkins Bloomberg School of Public Health, Baltimore, and was undertaken in collaboration with the National Society for the Prevention of Blindness (Nepal Netra Jyoti Sangh), Kathmandu, Nepal. The original vitamin A supplementation trial was carried out under Cooperative Agreement No DAN 0045-A-5094 between the Office of Nutrition, US Agency for International Development, Washington, and the Johns Hopkins University, as a joint undertaking of the Dana Center for Preventive Ophthalmology and the National Society for the Prevention of Blindness, Kathmandu, Nepal, with in-kind (provision of supplements) and technical (nutrient potency analyses) assistance from Task Force Sight and Life (formerly of Roche, Basel, Switzerland, now Sight and Life, DSM, Basel, Switzerland). The funding agencies had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships that could appear to have influenced the submitted work.

Ethical approval: The study was jointly 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.

Data sharing: No additional data available.

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What is already known on this topic

Purulent (discharging) middle ear infection and resultant hearing loss are a public health burden in low income countries

Vitamin A supplementation can reduce childhood mortality in undernourished societies, presumably by attenuating severity of infection

Experimental, mechanistic, and epidemiological data suggest that vitamin A deficiency may increase the risk of middle ear infection

What this study adds

Risk of hearing loss by early adulthood increases with the number of prevalent episodes of ear discharge in the preschool years

Preschool vitamin A supplementation does not affect the prevalence of ear discharge in early childhood

Preschool vitamin A supplementation reduces the risk of hearing loss in later life associated with ear discharge in the preschool years

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Accepted: 14 October 2011

Cite this as: *BMJ* 2012;344:d7962

Tables

Table 1| Household characteristics of adolescents and young adults at time of original trial and follow-up study by supplement allocation in Sarlahi, Nepal, 2006-8

Characteristics	No (%) in vitamin A group (n=1259)	No (%) in placebo group (n=1119)
Baseline		
Higher caste (Brahmin or Chettri)	293 (23.3)	224 (20.0)
Literate head of household	581 (46.1)	502 (44.9)
Occupation of head of household*:		
Farmer	822 (65.3)	812 (72.6)
Labourer	219 (17.4)	195 (17.4)
Private, business, or government	218 (17.3)	112 (10.0)
Head of household completed secondary school***:	83 (6.6)	100 (8.9)
>1 living room in house	669 (53.1)	588 (52.5)
Tube well water source	625 (49.6)	559 (50.0)
Latrine in home	71 (5.6)	68 (6.1)
Ownership:		
Watch	343 (27.2)	296 (26.5)
Land	990 (78.6)	913 (81.6)
Bicycle	273 (21.7)	237 (21.2)
Radio	318 (25.3)	259 (23.1)
Follow-up		
Pahadi ethnic group	697 (55.8)	577 (51.9)
>1 living room in house	1032 (82.6)	934 (84.1)
Tube well water source	990 (79.2)	903 (81.4)
Latrine in home	302 (24.2)	266 (24.0)
Ownership:		
Watch	804 (64.5)	700 (63.1)
Land	1058 (84.6)	911 (82.2)
Bicycle	914 (73.1)	808 (72.9)
Radio	591 (47.3)	563 (50.8)

Baseline variables missing for literacy (placebo n=1). Missing data on follow-up variables: ethnic group (vitamin A=10, placebo=8), rooms (vitamin A=9, placebo=8), water source (vitamin A=9, placebo=9), latrine (vitamin A=9, placebo=10), watch ownership (vitamin A=12, placebo=10), land ownership (vitamin A=9, placebo=11), bicycle ownership (vitamin A=9, placebo=10), radio ownership (vitamin A=9, placebo=10).

*P<0.05 by χ^2 test.

***P<0.001 by χ^2 test.

Table 2| Personal characteristics of adolescents and young adults at time of original trial and follow-up study by supplement allocation in Sarlahi, Nepal, 2006-8

Characteristics	No (%) in vitamin A group (n=1259)	No (%) in placebo group (n=1119)
Baseline		
Sex:		
Male	740 (58.8)	678 (60.6)
Female	519 (41.2)	441 (39.4)
Age at baseline (months):		
<12	266 (21.1)	232 (20.7)
12-60	993 (78.9)	887 (79.3)
No of visits with capsule administered directly:		
≤2	8 (0.6)	5 (0.5)
3-4	345 (27.4)	300 (26.8)
5	906 (72.7)	814 (72.7)
MUAC z score at baseline visit*:		
<−2	286 (22.7)	267 (23.9)
≥−2	972 (77.3)	849 (76.1)
Prevalent episodes of ear discharge†:		
0	1015 (80.6)	904 (80.8)
1	130 (10.3)	119 (10.6)
2	45 (3.6)	39 (3.5)
3	28 (2.2)	24 (2.1)
4	31 (2.5)	19 (1.7)
5	10 (0.8)	14 (1.3)
Follow-up		
Literate	915 (76.2)	776 (74.3)
Occupation‡:		
In-home	144 (12.0)	117 (11.2)
Farmer	267 (22.2)	277 (26.5)
Labourer	156 (13.0)	146 (14.0)
Private, business, or government	139 (11.6)	83 (8.0)
Student	495 (41.2)	421 (40.3)
Completed secondary school	449 (37.4)	366 (35.0)
Married	347 (28.9)	325 (31.1)

MUAC=mid-upper arm circumference.

Missing data for baseline variables: arm circumference (placebo n=3 and vitamin A n=1), ear discharge episode reports (placebo n=250 and vitamin A n=257).

Missing data on follow-up variables: literacy, marital status, occupation and education (placebo n=74 or 75 and vitamin A n=58 for each).

*MUAC z score calculated using 2006 WHO child growth standards.[50]

†Positive weekly reports of ear discharge in child collected by parental history every four months during original trial, 1989-91.

‡P<0.05 by χ^2 test.

Table 3| Odds ratios and absolute risk differences for failure of hearing screening test* among adolescents and young adults by preschool allocation of supplements in Sarlahi, Nepal, 2006-8

Supplement allocation	Total No	No (%)	Odds ratio† (95% CI)	% absolute risk difference† (95% CI)
Overall:	2373	278 (11.7‡)	—	—
Placebo	1117	134 (12.0)	1.00	—
Vitamin A	1256	144 (11.5)	0.97 (0.69 to 1.35)	−0.3 (−3.9 to 3.2)
No ear discharge:				
Placebo	902	67 (7.4)	1.00	—
Vitamin A	1012	88 (8.7)	1.17 (0.78 to 1.76)	1.2 (−1.9 to 4.2)
Any ear discharge:				
Placebo	215	67 (31.2)	1.00	—
Vitamin A	244	56 (23.0)	0.71 (0.44 to 1.14)	−6.8 (−16.4 to 2.7)

*Defined as not responding to a 30 dB tone in either ear at frequencies 0.5, 1, 2, 4, or 8 kHz.

†Estimates account for cluster randomised design of supplement allocation in original trial (1989-91) using generalised estimating equations method.[18]

‡95% confidence interval 10.4% to 13.0%.

Table 4| Odds ratios and absolute risk differences for hearing loss* among adolescents and young adults by preschool supplement allocation in Sarlahi, Nepal, 2006-8

Supplement allocation	Total No	No (%)	Odds ratio‡ (95% CI)	% absolute risk difference‡ (95% CI)
Overall:	2370	140 (5.9†)	—	—
Placebo	1116	72 (6.5)	1.00	—
Vitamin A	1254	68 (5.4)	0.83 (0.62 to 1.12)	−1.0 (−2.7 to 0.7)
No ear discharge:				
Placebo	902	30 (3.3)	1.00	—
Vitamin A	1012	36 (3.6)	1.07 (0.64 to 1.80)	0.2 (−1.5 to 1.9)
Any ear discharge:				
Placebo	214	42 (19.6)	1.00	—
Vitamin A	242	32 (13.2)	0.58 (0.37 to 0.92)	−7.2 (−13.0 to −1.4)

*Defined as mean of air conduction threshold values at 0.5, 1, 2, and 4 kHz ≥30 dB in worse affected ear among participants who failed hearing screening test.
†95% confidence interval 5.0% to 6.9%.
‡Odds ratio and absolute risk difference estimates account for cluster randomised design of supplement allocation in original placebo controlled vitamin A trial (1989-91) using generalised estimating equations method.[18]

Table 5| Adjusted odds ratios for tympanometric dysfunction* among adolescents and young adults by preschool supplement allocation (n=2364) in Sarlahi, Nepal, 2006-8

	Odds ratio† (95% CI)		
Supplement allocation	**Abnormal peak height‡**	**Abnormal gradient**	**Abnormal volume**
Overall:			
Placebo	1.00	1.00	1.00
Vitamin A	0.83 (0.67 to 1.03)	0.97 (0.70 to 1.35)	0.95 (0.69 to 1.31)
No ear discharge:			
Placebo	1.00	1.00	1.00
Vitamin A	0.85 (0.65 to 1.10)	1.13 (0.71 to 1.79)	0.82 (0.56 to 1.20)
Any ear discharge:			
Placebo	1.00	1.00	1.00
Vitamin A	0.83 (0.52 to 1.31)	0.89 (0.51 to 1.53)	1.45 (0.94 to 2.25)

*Defined as abnormal low or high peak height (<0.3 or >1.4 millimho), an abnormally wide gradient or low or high volume (<0.6 or >1.5 cm^3).

†Estimates account for cluster randomised design of supplement allocation using generalised estimating equations method and are adjusted for sex, age (months), occupation of head of household, and caste of household during original trial.

‡Missing data for peak height (n=5) and gradient (n=4).

Figures

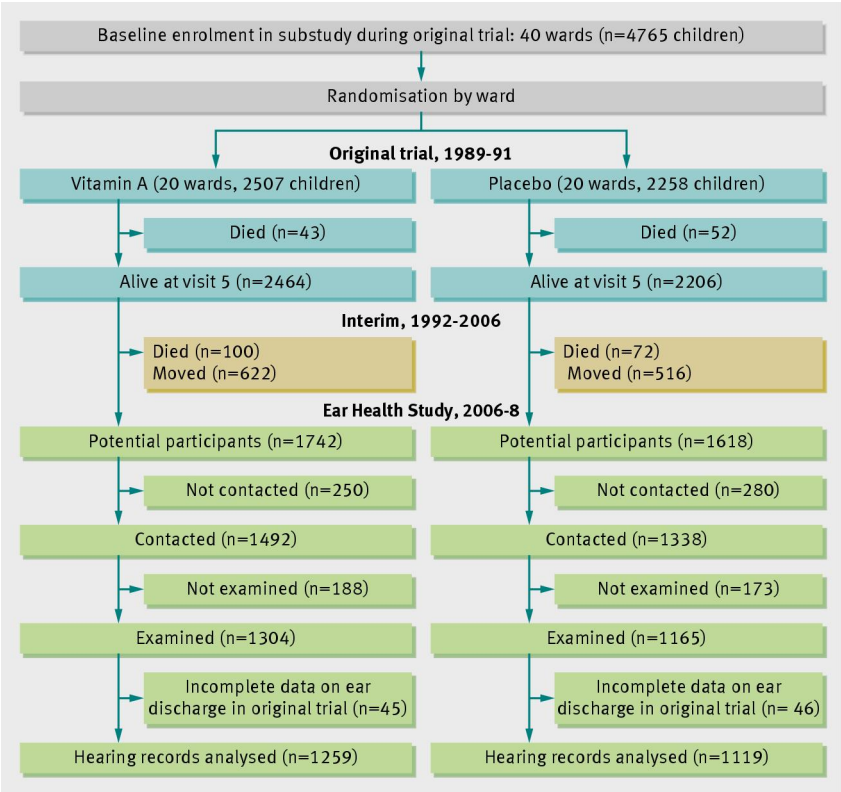

Fig 1 Flow of participants through trials

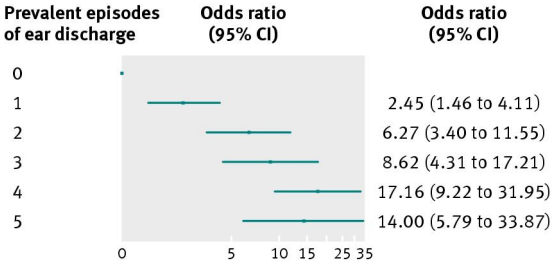

Fig 2 Relative odds of hearing loss in adolescents and young adults by reported frequency of ear discharge in preschool years, Sarlahi, Nepal 2006-8. Odds ratios (95% CI) expressed on natural log scale. Hearing loss defined as mean of air conduction threshold values at 0.5, 1, 2, and 4 kHz ≥30 dB in worst affected ear