Markers of inflammatory status are associated with hearing threshold in older people: findings from the Hertfordshire ageing study

CARL ANTON VERSCHUUR1, APHRA DOWELL2, HOLLY EMMA SYDDALL3, GEORGIA NTANI3, SHIRLEY J. SIMMONDS3, DANIEL BAYLIS3, CATHARINE R. GALE3, BRONAGH WALSH4, CYRUS COOPER3, JANET M. LORD5, AVA NAHIE SAYER3

1Hearing and Balance Centre, Institute of Sound and Vibration Research, University of Southampton, Highfield, Southampton SO17 1BJ, UK
2Audiology Department, Kent and Canterbury Hospital, Kent, UK
3MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK
4Faculty of Health Sciences, University of Southampton, Southampton, UK
5MRC Centre for Immune Regulation, University of Birmingham, Birmingham, UK

Address correspondence to: C. A. Verschuur. Tel: (+44) 23 8059 7601; Fax: (+44) 23 8059 4981. Email: cav@isvr.soton.ac.uk

Abstract

Background: age-related hearing loss is a common disabling condition but its causes are not well understood and the role of inflammation as an influencing factor has received little consideration in the literature.

Objective: to investigate the association between inflammatory markers and hearing in community-dwelling older men and women.

Design: cross-sectional analysis within a cohort study.

Setting: the Hertfordshire Ageing Study.

Participants: a total of 343 men and 268 women aged 63–74 years on whom data on audiometric testing, inflammatory markers and covariates were available at follow-up in 1995.

Main outcome measures: average hearing threshold level (across 500–4,000 Hz) of the worst hearing ear and audiometric slope in dB/octave from 500 to 4,000 Hz.

Results: older age, smoking, history of noise exposure and male gender (all $P < 0.001$) were associated with higher mean hearing threshold in the worse ear in univariate analysis. After adjustment for these factors in multiple regression models, four measures of immune or inflammatory status were significantly associated with hearing threshold, namely white blood cell count ($r = 0.13$, $P = 0.001$), neutrophil count ($r = 0.13$, $P = 0.002$), IL-6 ($r = 0.10$, $P = 0.05$) and C-reactive protein ($r = 0.11$, $P = 0.01$). None of the inflammatory markers was associated with maximum audiometric slope in adjusted analyses.

Conclusions: markers of inflammatory status were significantly associated with degree of hearing loss in older people. The findings are consistent with the possibility that inflammatory changes occurring with ageing may be involved in age-related hearing loss. Longitudinal data would enable this hypothesis to be explored further.

Keywords: hearing, age-related hearing loss, presbycusis, inflammation, ageing, older people, elderly
**Introduction**

Age-related hearing loss (presbycusis) is a common disabling condition worldwide which has a major impact on the ability of individuals to function in everyday life [1]. However, the biological mechanisms underlying presbycusis remain unknown. One possibility is that age-related hearing loss is mediated by the effect of inflammatory processes on the hearing system, particularly the cochlea. Lifestyle factors such as smoking and a high-fat diet are associated with hearing loss in older people [2]; it is possible that these factors impact on hearing as an indirect consequence of cardiovascular disease affecting the blood supply to the cochlea, or via a direct effect of inflammatory processes on the cochlea. There is known to be a relationship between hearing loss and inflammatory diseases such as diabetes [3] and cardiovascular disease [4]. Chronic changes in the immune response have been shown to be implicated in other neurological disorders such as Alzheimer’s disease [5]. Sudden onset hearing loss can be caused by acute inflammation [6]. A link between vascular pathology, immune function and experimental presbycusis has been identified in animal studies [7, 8] while damage to the hearing mechanism from hypoxia or noise damage has been shown to be mediated by cytokines in the inner ear [9]. There is evidence of cytokine production by fibrocytes, the stria vascularis and spiral ganglion cells [10]. Such evidence suggests the possibility that chronic age-related changes in inflammatory status, known as inflamming [11, 12], could cause, or accelerate, long-term damage to the hearing system with age. To the authors’ knowledge, no study to date has explored the relationship between inflammatory changes in older people and presbycusis. If such an association is found, this would lead both to potential interventions to target the effects of inflammation and to new avenues of basic research to help to define the biological mechanism of presbycusis.

We hypothesised that inflammatory status would be associated with hearing threshold in older people, independently of other important factors such as age, gender or noise exposure. The data collected for the Hertfordshire Ageing Study (HAS) [13] provided an opportunity to explore this hypothesis.

**Methods**

The HAS is a birth cohort study established to investigate the life course determinants of ageing which has been described in detail previously [13, 14]. From 1911 to 1948, midwives collected detailed records on infants born in Hertfordshire, UK. There were 6,803 live singletons born in North Hertfordshire between 1920 and 1930. With the help of the National Health Service Central Register, 1,428 who still lived there in 1995 were traced and 824 (58%) of the traced people agreed to a home interview. Information on medical history and lifestyle, including noise exposure, smoking and alcohol consumption was obtained. After interview, 717 men and women attended a clinic for detailed characterisation of ageing in a range of systems including hearing. Inter- and intra-observer reliability studies were carried out at regular intervals during the fieldwork to ensure comparability of measurements within and between observers. The study had ethical approval from the Hertfordshire and Bedfordshire Local Research Ethics Committee and all participants provided informed consent.

**Hearing**

Trained researchers assessed hearing in 714 individuals using the Hughson–Westlake method of pure-tone manual audiometry [15]. Audiometric thresholds were measured by air conduction at four frequencies (500, 1,000, 2,000 and 4,000 Hz) during the session. The main outcome variables were the average hearing threshold and audiometric slope. The average hearing threshold was the mean threshold value at 500, 1,000, 2,000 and 4,000 Hz by air conduction for the worse hearing ear, with higher values indicating more hearing loss. Audiometric slope was defined as the difference between 4,000 and 500 Hz thresholds divided by three; this was computed for each ear separately and the value for the ear with the steepest slope was taken. This measure served as a proxy measure for high-frequency hearing loss as 4,000 Hz threshold on its own was not normally distributed and was unable to be transformed to a normal distribution using standard statistical transformations. Higher values indicate worse high frequency thresholds compared with low-frequency thresholds. Thirty individuals in whom the tympanic membrane could not be observed and a further 73 with an asymmetric hearing loss (defined as an absolute difference of more than 20 dB between the audiometric thresholds of the right and left ear at two or more audiometric frequencies) were excluded from the study since it was likely that factors other than presbycusis had played a part in their hearing loss. Exclusion of those with asymmetric loss meant that choice of worse-hearing ear rather than better-hearing ear was unlikely to have had a large effect on results. Exclusion of data based on these criteria yielded a final sample of 611.

**Inflammatory status**

Blood samples were taken and initial tests included erythrocyte sedimentation rate (ESR) and white blood cell count with differential numbers of neutrophils, lymphocytes and monocytes. Stored serum has been used subsequently to measure additional inflammatory markers using multiplex technology including interleukins (IL-1, IL-6 and IL-10) and C-reactive protein (CRP).

**Other covariates**

Data on demographic and lifestyle characteristics including age, gender, and health behaviour were ascertained by
questionnaire. Noise exposure history was determined via two questions. The first question was ‘How long altogether have you worked in noisy places where you had to shout to be heard?’ with possible answers being ‘Never’, ‘Up to 5 years’ ‘More than 5 years’. The second was a yes/no question: ‘During your lifetime have you fired more than a total of 10 rounds from a shotgun or military rifle (not counting a 0.22 rifle)?’ Smoking was ascertained via the question ‘Have you ever smoked?’ Alcohol consumption was determined via the question ‘how often do you drink alcohol?,’ with six response options ranging from ‘never’ to ‘5–7 times a week’.

### Statistical analysis

Data were analysed using Stata version 11 [16]. Variables were assessed for normality and non-normally distributed variables were transformed using either a loge transformation (average hearing threshold, ESR, WBC, neutrophil counts, lymphocyte counts, IL-1b, IL-6, CRP) or a Fisher–Yates transformation (IL-10). Univariate analyses were firstly carried out to explore the associations between hearing threshold and audiometric slope with age, gender, smoking, alcohol consumption and noise exposure. Subsequently, univariate analyses were carried out to explore the associations between each inflammatory marker in turn and each of the two hearing outcomes. This was followed by multiple linear regression to determine whether any identified associations between hearing and the inflammatory markers were independent of age, gender, smoking, alcohol and noise exposure. To enable a consistent presentation of magnitudes and directions of association between hearing and inflammatory markers (irrespective of whether the hearing or inflammatory markers had been transformed), the results of the multiple linear regression analyses were presented as partial correlation coefficients. All analyses were carried out for men and women combined.

### Results

The demographic, lifestyle, inflammatory and hearing characteristics of the HAS participants who were included in this analysis are shown in Supplementary data Appendix 1, in Age and Ageing online. The average age of the study participants was 67.6 years and 56% of participants were male. Median worse-ear hearing threshold level (henceforth referred to as hearing threshold) was 26.25 dB HL with an inter-quartile range of 20–35 dB. Of the 611 participants, 131 (21.4%) had worse-ear hearing within normal limits (better than 20 dB HL); 364 were in the ‘mild hearing loss’ category (20–39 dB HL), 112 (18.3%) had moderate hearing loss (40–69 dB HL) and 4 (0.7%) had severe or profound hearing loss (70 dB HL or worse). Mean audiogram slope was 8.56 dB with a standard deviation of 6.58. Univariate associations between hearing threshold and maximum audiogram slope and age, gender, smoking, alcohol consumption and exposure to noise are shown in Table 1. Older age, male gender, having ever smoked, exposure to noise at work and having fired more than 10 rounds were associated with higher average hearing threshold in the worst ear (i.e. hearing was worse). There was no association between hearing threshold and alcohol consumption. Older age, male gender, ever smoking, alcohol consumption of once a week or more and noise exposure were all associated with higher (steeper) maximum audiometric slope (i.e. worse hearing at high frequencies compared with low).

Table 2 shows the associations between hearing threshold and each inflammatory or immune marker, with and without adjustment for age, gender, smoking and noise exposure. Hearing threshold was significantly associated ($P < 0.05$) with white blood cell count ($r = 0.13$, $P = 0.001$), neutrophils ($r = 0.13$, $P = 0.002$), IL-6 ($r = 0.10$, $P = 0.05$) and CRP ($r = 0.11$, $P = 0.01$), but not ESR ($r = 0.02$, $P = 0.56$), lymphocytes ($r = 0.07$, $P = 0.08$), monocytes ($r = 0.06$, $P = 0.13$), IL-1b ($r = −0.09$, $P = 0.07$) or IL-10 ($r = −0.01$, $P = 0.87$). Audiometric slope was not associated with any inflammatory markers after adjustment for the effects of gender, smoking status, alcohol consumption and noise exposure (Table 3). Re-analysis of data excluding those with head colds at time of data collection ($n = 17$) made no difference to the pattern of associations. We also repeated the analysis for each inflammaging variable (significantly associated with hearing loss in the primary analysis) categorised into thirds; again, pattern of associations with hearing loss remained unaltered.

### Discussion

The aim of the study was to investigate the cross-sectional relationships between inflammatory markers and hearing among community-dwelling older people. We have demonstrated that increased levels of certain inflammatory markers are associated with worse hearing after adjustment for other known influences on hearing such as age, smoking, alcohol and previous noise exposure. Specifically, a higher white blood cell count, neutrophil count, IL-6 level and CRP level were associated with worse overall hearing threshold in the worst hearing ear. This supported our hypothesis that there would be associations between inflammatory markers and hearing in older adults.

As far as we are aware, this is the first piece of evidence from a study in a human population to support a link between inflammation and presbycusis. The findings are consistent with the possibility that the age-related increase in basal inflammatory status, inflamming [12], is a causal factor for age-related hearing loss, although a causal link cannot be established with these cross-sectional data. An alternative explanation is that acute infections causing a rise in inflammatory markers underlie the observed associations.
Table 1. Univariate associations between the main outcomes and anthropometric, lifestyle characteristics and previous exposure to noise

<table>
<thead>
<tr>
<th>Age at clinic (years)</th>
<th>Alcohol consumption</th>
<th>Gender</th>
<th>Ever regular smoker</th>
<th>Exposure to noise at work</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.03 (1.02 to 1.05)</td>
<td>1.17 (1.10 to 1.26)</td>
<td>Males</td>
<td>1.17 (1.09 to 1.25)</td>
<td>1.17 (1.03 to 1.25)</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.21 (~0.01 to 0.44)</td>
<td>6.65 (5.73 to 7.56)</td>
<td>2.18 (1.10 to 3.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Associations between log transformed average hearing threshold before and after adjusting for cofounders

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted Regression coefficient (95% CI)</th>
<th>P-value</th>
<th>AdjustedP Regression coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average systolic bp (mmHg)</td>
<td>0.01 (~0.07 to 0.09)</td>
<td>0.72</td>
<td>0.03 (~0.05 to 0.11)</td>
<td>0.41</td>
</tr>
<tr>
<td>Average diastolic bp (mmHg)</td>
<td>0.06 (~0.02 to 0.14)</td>
<td>0.11</td>
<td>0.05 (~0.02 to 0.13)</td>
<td>0.17</td>
</tr>
<tr>
<td>ESR</td>
<td>-0.01 (~0.09 to 0.07)</td>
<td>0.82</td>
<td>0.02 (~0.06 to 0.10)</td>
<td>0.56</td>
</tr>
<tr>
<td>WBC</td>
<td>0.16 (0.08 to 0.24)</td>
<td>&lt;0.001</td>
<td>0.13 (~0.05 to 0.20)</td>
<td>0.007</td>
</tr>
<tr>
<td>Neutrophil counts</td>
<td>0.16 (0.08 to 0.24)</td>
<td>&lt;0.001</td>
<td>0.13 (~0.05 to 0.20)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>-0.01 (~0.01 to 0.15)</td>
<td>0.09</td>
<td>0.07 (~0.01 to 0.15)</td>
<td>0.08</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.12 (0.04 to 0.20)</td>
<td>&lt;0.001</td>
<td>0.06 (~0.02 to 0.14)</td>
<td>0.13</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.05 (~0.13 to 0.03)</td>
<td>0.21</td>
<td>0.04 (~0.12 to 0.03)</td>
<td>0.28</td>
</tr>
<tr>
<td>IL-1b (pg/mL)</td>
<td>-0.13 (~0.23 to 0.03)</td>
<td>0.01</td>
<td>0.09 (~0.18 to 0.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>0.13 (0.03 to 0.24)</td>
<td>0.01</td>
<td>0.1 (0.00 to 0.20)</td>
<td>0.05</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>0.1 (0.00 to 0.19)</td>
<td>0.05</td>
<td>0.01 (~0.13 to 0.11)</td>
<td>0.87</td>
</tr>
<tr>
<td>CRP (pg/mL)</td>
<td>0.11 (0.03 to 0.20)</td>
<td>0.01</td>
<td>0.1 (0.02 to 0.18)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

All predictors were standardised to have a mean of zero and standard deviation of one (on the raw or log scale as appropriate). The regression coefficients represent the standard deviation score change in the outcome variable per standard deviation in the predictor variable.

*Adjusted for age, sex, smoking status, exposure to noise at work and ‘fired 10’.

However, in such a large community-dwelling cohort of generally healthy people, this is unlikely.

IL-6 and CRP are related directly to inflammatory status and have been shown to be useful markers of in inflamming [12]. It is noteworthy that associations were found between IL-6 and CRP and hearing threshold in spite of some limitations in the inflammatory status data. For example, there was no information available on time of day of blood samples, an important consideration given that inflammatory markers are subject to diurnal variations [17]. However, it is likely that these factors would only have diluted any association between inflammatory markers and hearing threshold, so the finding that there were significant independent associations is suggestive of a possible role of inflammation in presbycusis. We also found that re-analysis of the data for better-hearing ear, or without exclusion of symmetric loss yielded essentially the same profile of significant associations between markers of inflammation and hearing level. This potential mechanism for presbycusis is worthy of further research through longitudinal studies of human populations, and via more basic biological research, for example by modulating the effect of inflammation on hearing status in senescence-accelerated mice [18].

The effects of age, gender and noise exposure on hearing are well established in the literature [19]. The fact that these variables were found to be significantly associated with hearing threshold in this cohort of older people was unremarkable, although it does support the validity of the audiometric data. We also found that smoking, but not alcohol consumption, was associated with overall hearing
threshold, but there was an association between alcohol consumption and audiometric slope. This adds weight to previous evidence suggesting a link between smoking and presbycusis [2, 20], although it is less conclusive with respect to the role of alcohol consumption [21].

Our study had some limitations. First, the nature of the audiometric data collected in the Hertfordshire Ageing Study may have affected the validity of the audiometric slope measure in particular. Although testing conformed to standardised procedures [15], audiometric testing was only undertaken up to 4,000 Hz by air conduction. Age-related hearing changes generally occur first at high frequencies [22] so in future work a more sensitive hearing test should also include measures of threshold at 6,000 and 8,000 Hz, especially given the relatively ‘young’ age of the cohort (mean age 67 years). This might help to explain the absence of significant associations between audiometric slope and a range of measures that were found to correlate with overall hearing threshold, although it is possible that different mechanisms affect the two variables [22]. Second, it should also be noted that audiometric testing was undertaken in a clinic environment and not in anechoic conditions, so that background noise may have affected the results. Third, the absence of bone-conduction audiometry meant that conductive hearing loss could not be definitively excluded from the sample. However, the fact that significant associations were identified between hearing loss and its known predictors (such as age and gender) and inflammatory markers, despite possible limitations in data collection methods, suggests that these associations are likely to be robust.

A final limitation of our work is that we were only able to study men and women who were born in Hertfordshire and who were still resident in North Hertfordshire in 1994–95 and were willing to participate in the Hertfordshire Ageing Study. However, the Hertfordshire Ageing Study participants have been shown to be broadly comparable with the wider population of England and Wales [13]. Moreover, the associations we describe are from internal comparisons. Our results would only be biased if the associations between hearing and inflammatory status were significantly different among HAS participants and the wider population of England and Wales of similar age; this seems unlikely. We therefore suggest that our results should be generalisable to the wider population of older people in England and Wales.

### Conclusions

Our data support the novel hypothesis that inflammatory status is associated with age-related hearing loss. This could inform understanding of underlying mechanisms for this common and disabling condition and suggests a potential area for development of future interventions, as well as for more basic research into the biological mechanisms of presbycusis.

### Key points

- This is the first study to explore the relationship between inflammatory status and presbycusis.
- Hearing threshold (averaged across audiometric frequencies 500 to 4,000 Hz in the worse ear) was found to be significantly associated with inflammatory markers (white blood cell count, neutrophil count, CRP and IL-6) among participants in the Hertfordshire Ageing Study (HAS).
- These results are consistent with a possible causal link between inflammatory status and hearing loss among older people.
- Audiometric slope was not associated with markers of inflammatory status.
- Further work is required to investigate the causal link between inflammatory processes and age-related hearing loss.

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### Table 3. Associations between maximum audiogram slope before and after adjusting for confounders

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted models</th>
<th></th>
<th>Adjusted models*</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Regression coefficient (95% CI)</td>
<td>P-value</td>
<td>n</td>
<td>Regression coefficient (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Average systolic bp (mmHg)</td>
<td>605</td>
<td>−0.07 (−0.15 to 0.01)</td>
<td>0.08</td>
<td>603</td>
<td>−0.02 (−0.09 to 0.05)</td>
<td>0.67</td>
</tr>
<tr>
<td>Average diastolic bp (mmHg)</td>
<td>604</td>
<td>−0.07 (−0.01 to 0.15)</td>
<td>0.08</td>
<td>602</td>
<td>0.02 (−0.05 to 0.09)</td>
<td>0.50</td>
</tr>
<tr>
<td>ESR</td>
<td>594</td>
<td>−0.17 (−0.25 to −0.09)</td>
<td>&lt;0.001</td>
<td>592</td>
<td>−0.05 (−0.12 to 0.02)</td>
<td>0.18</td>
</tr>
<tr>
<td>WBC</td>
<td>604</td>
<td>0.09 (0.01 to 0.17)</td>
<td>0.02</td>
<td>602</td>
<td>0.05 (−0.02 to 0.12)</td>
<td>0.20</td>
</tr>
<tr>
<td>Neutrophil counts</td>
<td>604</td>
<td>0.1 (0.02 to 0.18)</td>
<td>0.01</td>
<td>602</td>
<td>0.06 (−0.01 to 0.13)</td>
<td>0.10</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>604</td>
<td>−0.01 (−0.09 to 0.07)</td>
<td>0.79</td>
<td>602</td>
<td>−0.01 (−0.08 to 0.06)</td>
<td>0.72</td>
</tr>
<tr>
<td>Monocytes</td>
<td>604</td>
<td>0.15 (0.07 to 0.23)</td>
<td>&lt;0.001</td>
<td>602</td>
<td>0.02 (−0.05 to 0.09)</td>
<td>0.57</td>
</tr>
<tr>
<td>Albumin</td>
<td>602</td>
<td>0.01 (−0.07 to 0.09)</td>
<td>0.81</td>
<td>600</td>
<td>−0.01 (−0.08 to 0.06)</td>
<td>0.83</td>
</tr>
<tr>
<td>IL-1β (pg/mL)</td>
<td>426</td>
<td>−0.1 (−0.19 to −0.00)</td>
<td>0.05</td>
<td>426</td>
<td>0 (−0.09 to 0.09)</td>
<td>0.97</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>372</td>
<td>0.07 (−0.04 to 0.17)</td>
<td>0.21</td>
<td>370</td>
<td>0.04 (−0.06 to 0.13)</td>
<td>0.45</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>449</td>
<td>0.32 (0.22 to 0.41)</td>
<td>&lt;0.001</td>
<td>447</td>
<td>0.03 (−0.08 to 0.14)</td>
<td>0.61</td>
</tr>
<tr>
<td>CRP (pg/mL)</td>
<td>572</td>
<td>0.02 (−0.06 to 0.11)</td>
<td>0.57</td>
<td>570</td>
<td>0.02 (−0.05 to 0.09)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

All predictors were standardised to have a mean of zero and standard deviation of one (on the raw or log scale as appropriate). The regression coefficients represent the standard deviation score change in the outcome variable per standard deviation in the predictor variable.

*Adjusted for age, sex, smoking status, alcohol consumption, exposure to noise at work and ‘fired 10’.
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Conflicts of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References


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