Association of inflammatory markers with hearing impairment: the English Longitudinal Study of Ageing

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Abstract (250 words)

Background. Hearing impairment is common at an older age and has considerable social, health and economic implications. With an increase in the ageing population, there is a need to identify modifiable risk factors for hearing impairment. A shared aetiology with cardiovascular disease (CVD) has been advanced as CVD risk factors (e.g. obesity, type 2 diabetes) are associated with a greater risk of hearing impairment. Moreover, low-grade inflammation is implicated in the aetiology of CVD. Accordingly, our aim was to investigate the association between several markers of inflammation - C-reactive protein, fibrinogen and white blood cell count - and hearing impairment.

Methods. Participants of the English Longitudinal Study of Ageing aged 50 to 93 were included. Inflammatory marker data from both wave 4 (baseline, 2008/09) and wave 6 (2012/13) were averaged to measure systemic inflammation. Hearing acuity was measured with a simple handheld tone-producing device at follow-up (2014/15).

Results. Among 4879 participants with a median age of 63 years at baseline, 1878 (38.4%) people presented hearing impairment at follow-up. All three biomarkers were positively and linearly associated with hearing impairment independent of age and sex. After further adjustment for covariates, including cardiovascular risk factors (smoking, physical activity, obesity, diabetes, hypertension, cholesterol), memory and depression, only the association with white blood cell count remained significant: odds ratio per log-unit increase; 95% confidence interval =1.46; 1.11, 1.93.

Conclusions. While white blood cell count was positively associated with hearing impairment in older adults, no relationships were found for two other markers of low-grade inflammation.
Introduction

Hearing impairment is common in older age, with more than half of the European population suffering from substantial hearing loss by age 80 years\(^1\). It is an important cause of disability\(^2\), with considerable social, economic and health implications\(^3\). Hearing loss represents a burden for individuals and health care systems, given that its management is costly, and it impacts on the economy owing to a loss in productivity and unemployment\(^4\). Moreover, hearing impairment is associated with dementia\(^5\), depression\(^6\), lower cognitive function\(^7\), quality of life\(^8\), and physical functioning\(^9\); themselves risk factors for premature mortality\(^10\). As age-related hearing loss is currently incurable, prevention is key, and there is a need to identify risk factors that may be subject to intervention.

Known risk factors for age-related hearing impairment include genetic predispositions\(^11\) and environmental exposures particularly noise, infections, and ototoxic drugs\(^12\), with emerging correlates being lower levels of insulin-like growth factor I\(^13\) and early life exposures as proxied by adult physical stature\(^14\). A vascular cause has also been hypothesized, linked to changes in the microcirculation of the cochlea and ischemic intracochlear injury\(^15\). Observational studies have found associations between cardiovascular disease (CVD) risk factors such as obesity\(^16\), diabetes\(^17\), smoking\(^18\), subclinical atherosclerosis\(^19\) and hearing loss. Inflammation is a hallmark of ageing\(^20\) and is associated with atherosclerosis\(^21\) and cardiovascular outcomes\(^22\) as well as a wide range of age-related diseases including altered physical functioning\(^23\) and dementia\(^24\). Chronic low-grade inflammation is termed “inflammageing”. Animal studies suggest a link between immune function, vascular pathology and hearing loss, by mechanisms involving disrupted vascular integrity in the cochlear stria vascularis and disturbed ion homeostasis of the endolymph\(^25\).

The relationship between circulating inflammatory markers and hearing has, however, been little studied in ageing humans and results are inconsistent\(^26-29\). Three studies\(^26-29\) report
cross-sectional associations between elevated markers of inflammation, namely white blood cell counts (WBCC), neutrophil count, interleukin-6 (IL-6) and C-reactive protein (CRP), and hearing impairment. A longitudinal study found no association between CRP, IL-6 and tumour necrosis factor-α (TNF-α) levels from a single time point and incident hearing impairment. However, a 10-year high CRP profile (long-term chronic inflammation) offered some predictive capacity for subsequent hearing impairment, although only in participants younger than 60 years at baseline. This constituted the basis for a 3-year double blind randomized controlled trial of the effect of aspirin on age-related hearing loss.

The aim of the present study was to examine the association between several markers of inflammation - CRP, fibrinogen and WBCC - and objectively measured hearing impairment up to 6 years later in a cohort of older adults.
Methods

The English Longitudinal Study of Ageing (ELSA) is an on-going, prospective study of a nationally representative sample of men and women living in England aged ≥50 years at recruitment in 2002/2003 (wave 1). Data are collected every two years via face-to-face interviews, and nurse visits every 4 years for the assessment of clinical and biomarker data. At most waves, a “refreshment” sample of new younger participants is included to remain representative of the population aged 50 and older. Ethical approval was granted from NHS Research Ethics Committees, and all participants provided verbal informed consent.

For our main prospective analysis, wave 4 (2008/2009) was considered as baseline. We also conducted a cross-sectional analysis at wave 6. The main analytical sample consists of participants aged 50 to 93 years old with complete data on biomarkers at wave 4 or wave 6, covariates at wave 4 and hearing test at wave 7. In a secondary analysis, we excluded participants who self-reported hearing at baseline. The selection of the prospective and cross-sectional analytical samples is presented in Figure 1.

Inflammatory biomarkers

At each nurse visit, a blood sample was drawn (available for 65% of the participants at wave 4 and 67% at wave 6). High-sensitivity serum CRP (mg/L) was analysed using the N Latex CRP mono Immunoassay on the Behring Nephelometer II Analyser (Dade Behring, Milton Keynes, UK). We excluded CRP values >20 (n=134 at wave 4 and n=112 at wave 6) because they are likely to reflect acute infection. Fibrinogen (g/L) was analysed on the Organon Teknika MDA 180 coagulation analyser (Organon Teknika, Durham, USA). WBCC was measured on a haematology-automated analyser (Abbott Diagnostics Cell-Dyn 4000 at wave 4 and Sysmex XE at wave 6). All analyses were conducted at the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK) and details on internal quality can be found in the Health Survey for England technical report as the methodology is the same as in ELSA. The number of
participants with available data for each biomarker and each wave is described in Supplemental Table 1.

Hearing acuity

The only available information on hearing acuity at baseline (wave 4) and at wave 6 was self-reported during the interview. Participants rated their hearing, including using hearing aid if wearing one, on a 5-point scale from ‘poor’ to ‘excellent’. From these responses, we identified participants with self-reported hearing impairment as rating ‘poor’ or ‘fair’. This self-reported measure has previously been shown to be accurate when compared with objectively measured hearing 33.

At follow-up (wave 7, 2014/2015), participants took part in an objective hearing test unless they refused, reported use of a cochlear implant, had an ear infection or were unable to do the test (in total, 12% of the sample). The Siemens HearCheck device™ 34 was used, which has shown good sensitivity (ranging from 78% to 92%) and acceptable to good specificity (ranging from 62 to 95%) to detect hearing loss (at any intensity level) compared to the gold standard measure of hearing performance, pure tone audiometry 34 35. HearCheck is a simple handheld appliance which produces three pure tones of mid-frequency (1 kHz), followed by three high-frequency (3 kHz) tones. Participants who wore hearing aids removed them for the test. The interviewer held the device against the participant’s ear (left, then right). Participants had to indicate when they heard a tone when a sound was made at three intensities (55, 35 and 20 dB HL at 1kHz and then 75, 55 and 35 dB HL at 3kHz). The main outcome, hearing impairment (including mild), was defined as hearing fewer than 6 tones in the best hearing ear, i.e. a hearing ‘threshold’ of 20dB HL at 1kHz and 35 dB HL at 3k Hz. Covariates
Smoking status (current, former, never), alcohol drinking (≥5 days a week vs <5 days a week) and leisure-time physical activity (5 levels from low to high) were self-reported at baseline. Cognitive function (memory) was assessed using a word-list learning test (immediate and delayed), producing a continuous score ranging 0-20 (higher score represents a better memory). Depressive symptoms were ascertained using the eight-item Center for Epidemiologic Studies Depressive CES-D scale, with ‘caseness’ defined as a score ≥4. Educational attainment was classified as low (compulsory schooling), medium (up to high school) and high (university degree or higher). Height and weight were measured directly during the nurse visit, and body mass index (BMI) was defined as the weight (kg) divided by height squared (m²). Cholesterol was assayed using the DAX Oxidase assay. High-density lipoprotein (HDL)-cholesterol analysis was carried out on an Olympus 640 analyser using the direct method. Total glycated haemoglobin (HbA1c) assay was measured using the Tosoh G7 analyser. Diabetes was defined as HbA1c ≥ 6.5% and/or self-reported doctor-diagnosed diabetes. Systolic and diastolic blood pressure (SBP and DBP) were measured with an Omron HEM-907 BP monitor three times in the sitting position after 5-min rest and leaving 1-min between each reading. An average of the second and third BP recordings was used. Hypertension was defined as presenting any of the following: SBP≥140, DBP≥90 mm Hg, or self-reported doctor-diagnosed hypertension.

**Statistical analysis**

For each of the three markers of inflammation (CRP, fibrinogen, WBCC), we averaged the two measurements of wave 4 and wave 6 to gain precision and better reflect chronic inflammation. Averaging two measurements may limit fluctuations due to measurement error or biologic variability. If only one measurement was available (33% of the sample), we used the one that was available and only excluded participants who were missing both
measurements. We also used this method for covariates BMI and HDL-cholesterol to limit missing values.

Baseline characteristics were compared between cases and non-cases of hearing impairment by means of t-test or chi-square. The distributions of CRP and WBCC were skewed, so these variables were natural log-transformed. Logistic regression models were fit to estimate the relationship (odds ratios [OR] and 95% confidence intervals CI) between inflammatory markers and hearing impairment. We conducted four sets of analysis. In the main longitudinal analysis (Longitudinal 1), the independent variable was long-term biomarker exposure (average wave 4 and wave 6) and the outcome was subsequent objective hearing loss at wave 7, adjusting for baseline (wave 4) self-reporter hearing. In a secondary longitudinal analysis (Longitudinal 2), we excluded participants with self-reported hearing impairment (i.e. rating their hearing as “fair” or “poor”) at baseline. We also conducted two cross-sectional analyses: using only wave 6 inflammatory biomarkers in relation to objective hearing impairment (Cross-sectional 1) and cross-sectional association between wave 6 inflammation markers and self-reported hearing impairment (Cross-sectional 2). In all four designs, various levels of adjustment were used. In models 1, we adjusted the estimates for baseline age, sex and self-reported hearing (for longitudinal 1 and 2 only). Models 2 further included smoking status (current, former, never), BMI (kg/m²), physical activity (5 levels), education (3 levels), memory (continuous score) and depression. Models 3 further included clinical cardiovascular risk factors that may be mediators: HDL-cholesterol, hypertension and diabetes. In cross-sectional analysis 1, we also included self-reported hearing at wave 6 in Model 4. Because of the strong association between smoking and both inflammatory markers (exposure) and hearing impairment (outcome), residual confounding may still occur when adjusting for smoking status and stratification can help better disentangle the association. Interactions with smoking were modelled by the cross-product terms. Potential
nonlinear relations were examined using restricted cubic spline transformations. All analyses were performed using Stata 14 (StataCorp, TX, USA).
**Results**

Among 4879 participants with a median age of 63 years (interquartile range 58-70), 1878 (38.4%) had a hearing impairment at follow-up (2014). Compared to those without hearing impairment, those with the condition were older, more likely to be men, have received basic education, live alone, be sedentary, have hypertension and diabetes, have higher BMI, lower HDL-cholesterol, and lower memory score (**Table 1**). They were also more likely to have higher levels of CRP, fibrinogen and WBCC. Compared to the participants included in this analysis (**Supplemental Table 2**), the ones who were not included were older, had poorer reported hearing, lower memory score, education and physical activity level, were more likely to smoke and to live alone. The average of two measurements was available for two-thirds of the sample for all three biomarkers, and the remaining third had either a measurement at wave 4 or wave 6 only (**Supplemental Table 1**).

In models 1 (age and sex), all three biomarkers were positively and linearly associated with odds of hearing impairment: CRP OR \(1 \text{log-unit increase} = 1.17; 95\% \text{ CI: 1.09, 1.25;}
\)
fibrinogen OR \(1_\text{g/L increase} = 1.26; 1.10, 1.44\); WBCC, OR \(1 \text{log-unit increase} = 1.93; 1.50, 2.49\) (**Figure 2A**). The relation was linear for all three biomarkers, as the cubic splines did not improve the model fit. In Model 2 (adding smoking, BMI, physical activity, memory, depressive symptoms, and education), the association with CRP (OR: 1.04; 0.96, 1.13) and fibrinogen (1.07; 0.93, 1.24) became non-significant, whereas the association with WBCC remained (OR Model 2: 1.47; 1.12, 1.93). Further addition of CVD risk factors in the model did not attenuate this association (OR Model 3: 1.46; 1.11, 1.93). BMI and smoking were positively associated with hearing impairment, and largely explained the association of fibrinogen and CRP with hearing impairment as the estimates were attenuated and became non-significant after inclusion of these two factors in the models. Memory displayed a strong inverse association with hearing loss.
There was a suggested interaction between smoking status and WBCC (p-interaction =0.07) and with CRP (p=0.12). The associations with hearing impairment were positive in the non-smoker group (OR Model 1: 1.20; 1.11, 1.29 for CRP, 1.30; 1.13, 1.49 for fibrinogen and 1.95; 1.49, 2.55 for WBCC), whereas there was essentially no association in the smoker group (Figure 2A). The main findings were replicated when we excluded participants with self-reported hearing impairment at baseline (longitudinal analysis 2, Figure 2B). Results from cross-sectional analysis 1 of wave 6 biomarkers with objective hearing impairment are also very similar (Figure 3A), even when adjusting for self-reported hearing (Model 4), whereas associations with self-reported hearing impairment (cross-sectional analysis 2) were all non-significant (Figure 3B).
Discussion

In a cohort study of English older adults, we found that three inflammatory markers investigated – CRP, fibrinogen and WBCC - were associated with age-related hearing loss in age and sex-adjusted models. The associations with CRP and fibrinogen were largely explained by BMI and smoking, whereas the association with WBCC was independent of these factors.

Only a few studies have examined the relationship between inflammation and hearing loss in older adults. Verschuur and colleagues found cross-sectional associations between raised WBCC and worse hearing in two UK samples, a national study of hearing and the Hertfordshire Ageing Study (HAS), where WBCC was the biomarker most strongly associated with hearing impairment compared to CRP and IL-6. Despite methodological differences due to the use of a simple hearing test device in our study as opposed to pure tone audiometry in the other studies, our study corroborates the cross-sectional association and extends those findings showing a prospective association between raised WBCC, measured on two occasions, and higher odds of hearing impairment 6 years later. Moreover, this association was apparent only in non-smokers, so the observed estimates are independent of smoking, which is a strong correlate of WBCC. A possible explanation is that, although generating an overall pro-inflammatory state, smoking has ambivalent effects on macrophage and can promote anti-inflammatory macrophage polarisation. Therefore, smoking could selectively inhibit the effects of inflammation (high circulating levels of white blood cells) on hearing impairment, explaining the absence of a relationship between inflammation and hearing loss in smokers.

CRP showed a strong cross-sectional association with hearing impairment in participants aged 40-69 years of the National Health and Nutrition Examination Survey.
(NHANES) in the US \(^{29}\), as well as with hearing threshold in the HAS but not with maximum audiogram slope \(^{27}\). The only longitudinal analysis conducted in 1073 participants from the Epidemiology of Hearing Loss Study (EHLS) \(^{28}\) found no association when CRP or cytokines were measured once at baseline. However, it was found that long-term (10 years) high levels of CRP were associated with the incidence of hearing impairment independent of obesity, smoking and alcohol use but only in people aged < 60y. In our study smoking and BMI appeared to explain most of the association between medium-term high CRP and hearing loss. Comparability between the two studies is limited by the difference in assessment (pure tone air- and bone-conduction audiometry at 7 frequencies in EHLS, a simple handheld device in ELSA) and by the longer time of follow-up in EHLS (20 years).

Reducing fibrinogen levels in the circulation has been shown to be a promising therapy for idiopathic sudden sensorineural hearing loss, as fibrinogen increases blood viscosity and can reduce the blood flow into the cochlea \(^{41}\). However, the relationship between fibrinogen and age-related hearing loss has not been previously investigated. The association observed in our study was largely explained by lifestyle and CVD risk factors.

The identified factors involved in the pathology of age-related hearing loss include damage and loss of cochlear hair cells, damage of neural elements (loss of auditory nerve function, loss of spiral ganglion neurons in the cochlea) and biochemical damage to the inner ear (degeneration of the stria vascularis) \(^{12,42}\). However, not all older people are affected by hearing loss and multiple factors can contribute to the deterioration of hearing, including vascular damage \(^{27}\). An unhealthy lifestyle, combined with low-grade chronic inflammation that accompanies ageing, can influence hearing via an effect on cardiovascular disease reducing the blood supply in the cochlea or via direct inflammatory damage on the cochlea and on the spiral ganglion cells \(^{27}\). Our study supports both these mechanisms, given that inflammation and several CVD risk factors such as smoking, physical inactivity and obesity...
were predictive of an increased risk of hearing impairment. Inflammageing-related diseases such as obesity, hypertension and type 2 diabetes have been linked to poorer hearing in previous studies. Moreover, our results and a large body of studies, including animal models, make a direct inflammatory role plausible in the aetiology of age-related hearing loss. First, inner ear disorders have been observed in autoimmune diseases such as lupus erythematosus or polyarthritis. Moreover, the recommended treatment of sudden sensorineural hearing loss are anti-inflammatory corticosteroids, and their effectiveness has been shown. The network of tight junctions between the stria vascularis cells in the cochlear lateral wall prevents blood flow into the intrastrial region, known as the “fluid-blood” barrier. However, it is now established that this barrier is permeable to immune response signalling and that stria vascularis cells release pro-inflammatory cytokines through the tight junction barrier, and that there can be inflammation in the cochlea. Mouse models suggest an important part of the cochlear response to age-related chronic hair cell degeneration is an immune response mediated by macrophages. The only marker of inflammation associated with hearing loss in our study was white blood cells, and this may be related to the important role of macrophages, a type of white blood cell. The other two markers studied here, CRP and fibrinogen, are downstream in the inflammation response and have been found not to be causally related to cardiovascular disease outcomes. Therefore we hypothesise that circulating cytokines such as IL-6 or TNF-α, that govern the inflammatory cascades upstream may be better predictors of hearing impairment.

The main strengths of this study are the well-characterised large nationally representative sample, followed up for 6 years and the inflammatory biomarkers measured at two-time points to increase accuracy and reflect chronic inflammation over 4 years. It is the first study to assess three inflammatory biomarkers prospectively in relation to hearing in such a large sample. However, the main limitation of our study is the assessment of hearing
function. First, hearing at baseline was self-reported, which is known to differ from audiometric hearing loss as people can deny their hearing loss; therefore participants with existing hearing problems at baseline are likely to have been included in the analysis. Moreover, compared to pure tone audiometry, the hearing test used has shown acceptable sensitivity and sensibility to detect mild to severe hearing loss but does not cover the same frequency range (the hearing test provides only two frequencies, 1kHz and 3 kHz at three intensities), which limits the comparison with existing studies and the interpretation of the findings to a certain extent. Pure tone audiometry is considered the gold standard to assess hearing sensitivity, measuring both air (at frequencies from 0.125kHz to 8 kHz) and bone (from 0.25 to 4 kHz) conduction hearing thresholds. The shape of the resulting audiogram informs on the disease such as conductive hearing loss (external and middle ear damage), or sensorineural hearing loss, typically at high frequency for age-related or noise-induced hearing loss (related to hair cell damage in the cochlea). However, even pure tone audiometry has limitations: it requires active cooperation from the patient, which can be problematic in elderly participants; moreover, it does not provide information about central auditory processing, nor the auditory processing of real-world signals such as conversations or music. Despite the limitation inherent to the HearCheck method, this hearing test has been used to assess hearing loss in the Health Survey for England, to provide the first up-to-date estimates of hearing impairment in the UK. In addition, the fact that the baseline and follow-up assessment of hearing performance are different is a methodological caveat as it does not allow us to assess incidence (new cases) of hearing loss. Another crucial information that was not available in our study is noise exposure. Finally, we had to exclude an important part of the sample who had missing data, and excluded participants were older and less healthy; therefore selection bias may have incurred, possibly leading to collider bias and to a more homogeneous population, thus distorting the association. However, despite the limitations
Presented, we observed enough variability in all our measurements, and believe that the generalisability of the associations should not be compromised. Moreover, we observed a strong association between WBCC and objective hearing impairment using different modelling and design approaches, which gives confidence in the robustness of our results.

In a cohort of English older adults, chronic inflammation measured by elevated WBCC, but not CRP or fibrinogen, was associated with hearing impairment. If results are replicated, monitoring and reducing the levels of inflammation alongside other cardiovascular risk factors has the potential to reduce the burden of age-related hearing loss.
References


Table 1. Baseline (2008) characteristics according to hearing impairment in 2014: the English Longitudinal Study of Ageing

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>No hearing impairment</th>
<th>Hearing impairment</th>
<th>P-value $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=4879</td>
<td>N=3001</td>
<td>N=1878</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.1 (8.02)</td>
<td>61.6 (6.65)</td>
<td>68.2 (8.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female n(%)</td>
<td>2670 (54.7%)</td>
<td>1731 (57.7%)</td>
<td>939 (50.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Degree</td>
<td>929 (19.0%)</td>
<td>682 (22.7%)</td>
<td>247 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>2861 (58.6%)</td>
<td>1790 (59.6%)</td>
<td>1071 (57.0%)</td>
<td></td>
</tr>
<tr>
<td>No qualifications</td>
<td>1089 (22.3%)</td>
<td>529 (17.6%)</td>
<td>560 (29.8%)</td>
<td></td>
</tr>
<tr>
<td>Living with partner</td>
<td>3564 (73.0%)</td>
<td>2290 (76.3%)</td>
<td>1274 (67.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depressive symptoms (CES-D≥4)</td>
<td>566 (11.6%)</td>
<td>325 (10.8%)</td>
<td>241 (12.8%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Memory score (0-20)</td>
<td>11.1 (3.23)</td>
<td>11.7 (3.06)</td>
<td>10.2 (3.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drinks alcohol daily</td>
<td>1029 (23.2%)</td>
<td>653 (23.7%)</td>
<td>376 (22.4%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td>0.054</td>
</tr>
<tr>
<td>Never smoker</td>
<td>1983 (40.6%)</td>
<td>1259 (42.0%)</td>
<td>724 (38.6%)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>2307 (47.3%)</td>
<td>1382 (46.1%)</td>
<td>925 (49.3%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>589 (12.1%)</td>
<td>360 (12.0%)</td>
<td>229 (12.2%)</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedentary</td>
<td>518 (10.6%)</td>
<td>223 (7.43%)</td>
<td>295 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>Moderately inactive</td>
<td>639 (13.1%)</td>
<td>370 (12.3%)</td>
<td>269 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Moderately active</td>
<td>1504 (30.8%)</td>
<td>926 (30.9%)</td>
<td>578 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>1060 (21.7%)</td>
<td>675 (22.5%)</td>
<td>385 (20.5%)</td>
<td></td>
</tr>
<tr>
<td>Very active</td>
<td>1158 (23.7%)</td>
<td>807 (26.9%)</td>
<td>351 (18.7%)</td>
<td></td>
</tr>
<tr>
<td>Self-reported hearing</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Excellent</td>
<td>994 (20.4%)</td>
<td>798 (26.6%)</td>
<td>196 (10.4%)</td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>1406 (28.8%)</td>
<td>1010 (33.7%)</td>
<td>396 (21.1%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>1633 (33.5%)</td>
<td>943 (31.4%)</td>
<td>690 (36.7%)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>700 (14.3%)</td>
<td>230 (7.66%)</td>
<td>470 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>146 (2.99%)</td>
<td>20 (0.67%)</td>
<td>126 (6.71%)</td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td>2394 (49.1%)</td>
<td>1325 (44.2%)</td>
<td>1069 (56.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>513 (10.5%)</td>
<td>272 (9.06%)</td>
<td>241 (12.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.2 (5.02)</td>
<td>28.0 (5.00)</td>
<td>28.5 (5.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.62 (0.43)</td>
<td>1.64 (0.45)</td>
<td>1.57 (0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L) $^b$</td>
<td>1.64 (1.60; 1.68)</td>
<td>1.53 (1.48; 1.58)</td>
<td>1.83 (1.76; 1.91)</td>
<td>&lt;0.001 $^c$</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.15 (0.5)</td>
<td>3.11 (0.49)</td>
<td>3.21 (0.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBCC ($10^9$ cell/L) $^b$</td>
<td>6.11 (6.06; 6.15)</td>
<td>5.98 (5.93; 6.04)</td>
<td>6.31 (6.23; 6.38)</td>
<td>&lt;0.001 $^c$</td>
</tr>
</tbody>
</table>

Values are mean (SD) or n (%) as appropriate

$^a$ p-value of the chi-square test (categorical variables) or t-test (continuous variables) of the difference between the cases and non-cases of hearing impairment at the end of follow-up

$^b$ geometric mean and 95% confidence interval

$^c$ t-test performed on natural log-transformed values
Figure 1. Flow of subjects into the two analytical samples, prospective (panel A) and cross-sectional (panel B), the English Longitudinal Study of Ageing, 2008.
* numbers non-mutually exclusive

The % given in parenthesis is the proportion of participants included at each selection step
Figure 2. Prospective associations between three inflammatory biomarkers (2008-2012) and odds of hearing impairment (2014), in the main analytical sample (panel A) and after exclusion of self-reported hearing impairment at baseline (panel B) the English Longitudinal Study of Ageing.
Estimates are multivariate odds ratios (OR) and 95% confidence interval (95% CI)

Model 1 includes baseline age, sex and self-reported hearing at baseline

Model 2: Model 1 + smoking, physical activity, BMI, memory score, education, depression

Model 3: Model 2 + cardiovascular risk factors: diabetes, hypertension, HDL-cholesterol
Figure 3. Cross-sectional associations between inflammatory biomarkers and odds of hearing impairment (panel A) objectively measured (1587 cases) and (panel B) self-reported (875 cases), the English Longitudinal Study of Ageing, n=4470

Estimates are multivariate odds ratios (OR) and 95% confidence interval (95% CI)

Model 1 includes age and sex

Model 2: Model 1 + smoking, physical activity, BMI, memory score, education, depression

Model 3: Model 2 + cardiovascular risk factors: diabetes, hypertension, HDL-cholesterol

Model 4: Model 3 + self-reported hearing