Relative risk of elevated hearing threshold compared to ISO1999 normative populations for Royal Australian Air Force male personnel

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Objective: This paper introduces a new method to calculate relative risks of elevated hearing thresholds, at various ages and frequencies, between a study population and ISO1999:2003: Annex A Screened, Annex B Unscreened and ISO1999 Section 5.3 adjustment for noise exposure using Annex A Screened data. We demonstrate this method on a study population of male Royal Australian Air Force personnel.

Study Design: Using a retrospective cohort design, hearing thresholds were assessed in 583 F-111 aircraft maintenance personnel, 377 technical-trade comparisons and 492 non-technical comparisons using pure-tone audiometry. A quantile regression model was used determine whether an association exists between median hearing thresholds and F-111 maintenance, adjusting for possible confounders. The new method involves using quantile regression models with bootstrapped standard errors to estimate percentiles for the study population and thus determine the probability of a greater than 25 dB hearing threshold. This was done for the three ISO datasets as follows; for the ISO1999 Annex A screened population data the formula provided allows the calculation of these probabilities. ISO1999 Annex B unscreened population data only provides the values for the 10th, 50th and 90th percentiles at ages 30, 40, 50 and 60 only, therefore it was necessary to fit a curve to these values in order to estimate the probabilities. For ISO1999 Section 5.3 adjustment for noise exposure population we used the Annex A screened population data plus the formula. The probabilities were then divided to give the relative risks of a greater than 25 dB hearing threshold, at various ages and frequencies.

Results: While no difference was observed between the three groups, the model identified a number of significant confounders, namely tinnitus, smoking, diabetes and the use of anti-depressant medications. Relative risks were high at frequencies 2 kHz and less for the study population of all ages compared to ISO A screened data. The increased relative risks at 4 and 6 kHz give the appearance of a “noise notch” for ages 30 and 40 years. The comparison with the ISO B unscreened data are significantly less than one for frequencies above 2 kHz, particularly for young men and greater than one less than 2 kHz. The relative risks for the comparison to the ISO A screened data with ISO 5.3 adjustments, are highest for young men decreasing with age, with the highest relative risk are at frequencies less than 2 kHz.

Conclusions: This paper demonstrates a new method for quantifying the probability of a clinically relevant hearing loss and the relative risk of the loss due to a risk factor. Prior to this, researchers were reduced to simplistic methods such as visual comparison of deciles which did not enable the estimation of risk. The new method can use all observed hearing thresholds per study participant, adjust for known confounding factors such age and gender, and calculate the relative risk of a clinically relevant increase in hearing threshold due to a risk factor of interest.
risk significantly greater than one indicates the likelihood of the adverse outcome is increased by exposure. In this paper we demonstrate a method for calculating the relative risk of a specified increase in hearing threshold at a given age and frequency, relative to normative population data.

Noise induced hearing loss (NIHL) is a permanent condition of the inner ear characterized by loss of auditory acuity, particularly in the 3–6 kHz range (Rabinowitz et al., 2006). NIHL remains a significant problem in industry, despite substantial research on the mechanisms of damage, availability of exposure limits for acceptable noise levels, and demonstration of effective programs for hearing loss prevention (Seixas et al., 2005). The most common objective for protecting workers from the auditory effects of occupational noise has historically been the preservation of hearing for speech discrimination (Prince et al., 1997), that is 0.5–3 kHz (Dobie, 1997). The effect of noise exposure is evident with pure-tone audiometry almost immediately, with the greatest reduction (International Organisation for Standardisation, 2003):

standard population data, and estimate hearing loss excess of that

1. ISO9999 Annex A (ISO A screened) otologically normal popu-
lation data provides a formula for the expected median value
of hearing thresholds relative to the median threshold at the
age of 18 years, and the percentiles above and below the
median value for the range of audiometric frequencies from
125 Hz to 8000 Hz, for populations of highly screened (i.e.
otologically normal) male and female persons of a given age
between 18 and 70 years inclusive (ISO A screened).
2. ISO9999 Annex B (ISO B unscreened) specifies hearing
thresholds of the 10th, 50th and 90th percentiles of an
unscreened population, by gender, at 30, 40, 50 and 60 years
of age for frequencies from 500 Hz to 6000 Hz.
3. ISO9999 Section 5.3 (ISO 5.3) provides a formula to be used
with either Annex A or B to determine the HT adjusted for level
of noise exposure and length of time exposed.

Various occupational studies have compared the hearing thresholds (HT) of noise exposed workers to ISO normative thresholds, although the analysis has sometimes been problematic. A consistent problem has been the determination of appropriate statistical methods due to the multiple observations per study participant, since each ear is measured at multiple frequencies. The multiple observations for each participant are likely correlated, thus standard statistical tests, such as t-test for example, will not give an accurate p-value. A number of approaches have been used to partially get around this issue by reducing the volume of data including:

1. Average HT over frequencies 1–6 kHz and compare graphically
to the ISO A screened median, also averaged over 1–6 kHz, at
d four ages 30–60 years (Jirojwong et al., 2005).
2. Correlate the observed HT at each frequency and compare to
the median of predicted thresholds (Kuronen et al., 2004).
3. Subtract ISO A screened median and then do t-test on HT
on each ear and each frequency separately (Wagstaff and Arva,
2009).
4. Subtract ISO A screened median and divide by upper/lower
standard deviation, then do t-test on HT on each ear and each
frequency separately (Toppila et al., 2011).
5. Reduce to four age groups, subtract the ISO A screened median
and divide by upper/lower sample standard deviation, then do
t-test on HT on both ears combined, for each frequency separa-
ately (Henselman et al., 1995; Royster et al., 1991; Steurer et al.,
1998).
6. Average HT over frequencies 3–8 kHz for each ear, subtract the
ISO A screened median, then do Mann—Whitney rank sum test
to compare males and females, and the Wilcoxon rank sum
to compare left and right ears (Schmuziger et al., 2006).
7. Subtract ISO B unscreened median, average over frequencies
1–4 kHz and both ears, then do ANOVA to compare mean HT
by noise exposure groups, race and years of military service
(Henselman et al., 1995; Royster et al., 1991; Steurer et al.,
1998).
8. Subtract an ISO median, average HT over frequencies groups,
then do ANOVA to compare frequency groups, left and right
ears and exposure groups (Henselman et al., 1995; Royster
et al., 1991; Steurer et al., 1998).
9. Dichotomize by defining the existence of a noise notch and use
a proportion test to compare to a different population (Bar-
low, 2011).
10. Dichotomize HT by choosing a cut-point between no/minimal
loss, and moderate/severe loss and then apply logistic regres-
sion to estimate effects of factors such as age, gender, medical
conditions and solvent exposure (Guest et al., 2010).
11. Dichotomize by defining material impairment to have occurred
if the average HT over a set of frequencies is greater than 25 dB,
and then do logistic regression to estimate the effects of factors
such as noise exposure (Prince, 2003; Prince et al., 1997).

There are a number of disadvantages with some of these methods. First, averaging reduces the variability present in the data and information is lost. Second, HTs are rarely normally distributed so t-test is likely not appropriate, and third, dichotomization may result in the dilution of the effect of the risk factor, since partici-
pants with moderate hearing loss have been divided between no/
minimal loss, and moderate/severe loss. Finally and perhaps most
importantly, standard non-parametric tests do not allow the esti-
mation of the effect of any other explanatory variables associated
with the outcome. In the case of hearing, occupational noise is just
one of many factors than can affect the incidence and degree of
elevated hearing thresholds. Presbycusis, the gradual hearing loss
associated with ageing, affects more than one-third of those over
75 years and is probably due to gradual cumulative loss of hair cells
and neurons ( Ganong, 2003). Other factors include gender
(International Organisation for Standardisation, 2000), diabetes
(Bainbridge et al., 2010; Frisina et al., 2006; Gopinath et al., 2009;
Tay et al., 1995), depression (Gopal et al., 2004; Monzani et al.,
2008), smoking (Gopinath et al., 2009; Nakaniishi et al., 2000),
alcohol consumption (Campo and Lataye, 2000), exposures to loud
noise (Jokitalo et al., 2006), and sudden explosive peaks of
impulse noise (May, 2000). The importance of adjusting an analysis for
confounding variable is highlighted by Agrawal et al. (2010).

To address these concerns we present a method which used quantile regression (Horowitz, 1998; Koenker and Bassett, 1978;
Weiss, 1988). This technique minimizes the sum of the absolute
value of residuals and can estimate percentiles at specified values of
the explanatory variables, whereas ordinary-least-squares linear
regression minimizes the sum of the squares of residuals and esti-
mates the mean at specified values of the explanatory variables. This
method is particularly appropriate for our purpose here since the
ISO datasets provide percentiles by age and gender, and quantile
regression allows us to estimate percentiles by age and gender. To accommodate the probable correlation between the multiple observations per person, bootstrapping is used. This technique is used to calculate standard errors and confidence intervals for estimates obtained from data for which either the distributional assumptions and/or the assumption of independence is not valid. The approach involves repetitive re-sampling from the dataset, and recalculating the estimate each time, to create an empirical distribution for the estimate. From this empirical distribution, there are a number of commonly used methods to calculate standard errors and confidence intervals. For hearing data with multiple observations per person, the sampling unit for each bootstrap replicate sample is at the person level (Efron and Tibshirani, 1993).

We demonstrate our method on a sample of Royal Australian Air Force (RAAF) male personnel whose hearing thresholds were assessed in using pure-tone audiometry in a study of F-111 fuel tank maintenance personnel and two comparison groups (D’Este et al., 2004). The Australian Defence Forces Entrance Medical Requirements specify the maximum allowable hearing threshold in either ear for all frequencies less than 8 kHz at enlistment is 25 dB. Since otologically normal means “free from all signs or symptoms of ear disease and from obstructing wax in the ear canal, and who has no history of undue exposure to noise” (International Organisation for Standardisation, 2000), it is unlikely that every member of the study population was otologically normal at enlistment. However, the existence of the entrance hearing requirement means that RAAF study population are screened to some extent compared to the general Australian population.

Aircraft maintenance technicians’ exposures to aircraft noise, jet fuel and other chemical exposures have been a recent focus for hearing loss research (Kaufman et al., 2005; Kim et al., 2005; Prasher et al., 2005). F-111 fuel tank maintenance workers experienced a particular risk to organic solvents: in F-111 aircraft, the fuel occupies the empty spaces between the plane metal structures and the sealant eventually degrades requiring periodic repair, which involves dissolving the original sealant and removing it (desealing) and then replacing it with new sealant (resealing). The RAAF performed four formal F-111 fuel tank Deseal/Reseal (DSRS) programs between 1975 and 1999, each involving a different range of hazardous substances, including jet fuel, organic solvents, epoxy resins and paint (D’Este et al., 2004; Guest et al., 2010). Between 2001 and 2004, we conducted a comprehensive, large-scale investigation on behalf of the Australian Department of Defence of all personnel involved in the DSRS activities in Australia and two contemporaneous comparison groups. We have previously reported on hearing loss in all three groups (Guest et al., 2010).

2. Material and methods

The Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP) was a retrospective cohort study investigating the possible association between DSRS activities and adverse health status. The methods have been reported previously in detail (Attia et al., 2006; Guest et al., 2010) and are briefly summarized here. The study involved a mailed postal questionnaire and a series of clinical assessments. Ethical approval to conduct the study was granted from the following institutional ethics committees: the Human Research Ethics Committee of the University of Newcastle, Australia, the Australian Defense Human Research Ethics Committee and the Australian Department of Veteran’s Affairs Human Research Ethics Committee.

2.1. Study population

The study consisted of an exposed population who had been involved in one or more of the four DSRS (the “exposed”) and two appropriate comparison groups (the “Richmond comparison” and “Amberley comparison”). DSRS exposure was confirmed via a mailed Exposure Questionnaire specifically developed for the study. Two comparison groups were obtained by sampling from the computerized Air Force Personnel Executive Management System: same base (RAAF Base Amberley, Queensland) who worked in non-aircraft maintenance jobs, and different base (RAAF Base Richmond, New South Wales) who conducted aircraft maintenance.

2.2. Measures

A physician, nurse and clinical psychologist performed a number of health assessments over a total of three to 4 h at one of eight offices of Health Services Australia. Pure-tone audiometry was undertaken to assess hearing by occupational health nurses who had received specific training in the conduct of all study procedures and were qualified to conduct pure-tone audiometry. Participants were screened using the Rey-15-item test (Rey, 1964) to examine the potential for inadequate effort during psychological testing and those with a score of eight or less, an indication of potentially unreliable results, were excluded from these analyses (Goldberg and Miller, 1986; Hiscock et al., 1994).

2.3. Hearing outcomes

An otoscopic examination was carried out to check the outer ear for any temporary obstruction in the ear canal that would prevent a valid result being obtained. Testing was not conducted on participants with evidence of an obstruction, those reporting exposure to high levels of noise in the previous 16 h and those suffering from temporary ailments that might affect hearing. Eight hearing thresholds were measured in each ear by pure-tone audiometry using an ascending/descending technique in 5-dB steps at the frequencies of 0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz in accordance with Australian Standard 1269.4:1998.

2.4. Risk factors

During the clinical examination, the existence of anxiety/ depression was assessed using the Kessler Psychological Distress Scale (K-10) which measures symptoms of anxiety and depression over the four weeks prior to the test. Higher scores indicate higher probability of having anxiety and depression (Andrews and Slade, 2001). Participants completed a postal questionnaire that included self-reported information on general health and well-being, and a variety of outcomes including alcohol intake, smoking history, diagnosis of diabetes and military postings. Alcohol intake was coded to four categories: teetotaler/safe, moderate, hazardous binge, and hazardous-chronic according to The Australian Alcohol Guidelines (National Health and Medical Research Council, 2001). Smoking behaviour was grouped to three categories: never, former and current. Participants provided a list of medications regularly used which were subsequently coded by a research pharmacist to the World Health Organization’s Anatomical Therapeutic Chemical Classification. Anti-depressants, in particular selective serotonin reuptake inhibitors, were of interest as recent studies have confirmed the presence of serotonin in the cochlea and vestibule, which indicates that it may play a role in hearing (Tadros et al., 2007; Vicente-Torres et al., 2003). The civilian job history calendar was used to determine civilian exposure to organic solvents, lead, excess and impulse noise, where participants were classified as having an exposure if they had reported a civilian job for which the Finnish Job Exposure Matrix probability of exposure was greater than 20% (Kauppinen, 1998).
2.5. Exposure to noise

Participants were exposed to two sources of noise: job specific noise and noise from aircraft movements on the base. No estimates of noise exposure for job specific tasks or for individual participants were available; however, noise levels were available for the various aircraft types operating from the two bases. At the Amberley base the main fixed wing aircraft to operate were the F-111s which have two Pratt and Whitney TF-30 turbofan jet engines. Noise levels adjacent to an F-111 on the tarmac with one engine running on full power with after-burner and the second engine running a maximum military power is 130dBA. In addition there were two types of rotary wing aircraft; Blackhawk helicopters which have a single rotor and a single General Electric T700-GE-701C turbine engine and Chinook helicopters which have tandem rotors and two engines with after-burner and the second engine running a maximum military power is 130dBA. In addition there were two types of rotary wing aircraft; Blackhawk helicopters which have a single rotor and a single General Electric T700-GE-701C turbine engine and Chinook helicopters which have tandem rotors and two engines with after-burner and the second engine running a maximum military power is 130dBA.

ISO1999 Annex A screened population data

To calculate the probability of a hearing threshold of 25 dB or more we start with the following hearing threshold equation:

\[
T(u, a, g, f) = cu(g, f) + a(g, f)(a - 18)^2 + \Phi^{-1}(u) \left( \beta_u(g, f) + \gamma_u a(g, f)(a - 18)^2 \right), \quad \text{for } u \geq 0.5,
\]

\[
T(u, a, g, f) = c_1(g, f) + a(g, f)(a - 18)^2 + \Phi^{-1}(u) \left( \beta_1(g, f) + \gamma_1 a(g, f)(a - 18)^2 \right), \quad \text{for } u < 0.5.
\]

methods used to exclude variables that were not significant at the 0.1 level. Interaction terms (products of explanatory variables) were tested and retained in the model as necessary to increase the ability of the model to accommodate non-linear relationships.

Relative risks of a 25 dB or more increase in hearing threshold for the study population compared to the ISO thresholds were calculated by estimating the probability of a greater than 25 dB increase in hearing threshold with quantile regression models for a normal member of the study population and then dividing this probability by that for the ISO data, at various ages and frequencies. This was done for the three ISO datasets as follows:

ISO1999 Annex A screened population data

To calculate the probability of a hearing threshold of 25 dB or more we start with the following hearing threshold equation:

\[
u(T, a, g, f) = \Phi\left( T - cu(g, f) - a(g, f)(a - 18)^2 \right) / \left( \beta_u(g, f) + \gamma_u a(g, f)(a - 18)^2 \right), \quad \text{for } u \geq 0.5,
\]

\[
u(T, a, g, f) = \Phi\left( T - cl(g, f) - a(g, f)(a - 18)^2 \right) / \left( \beta_1(g, f) + \gamma_1 a(g, f)(a - 18)^2 \right), \quad \text{for } u < 0.5.
\]

At the Richmond base two types of fixed wing aircraft operate; the C-130 Hercules with four Allison turboprop engines and the Caribou with two Pratt and Whitney R-2000 14 cylinder radial engines. Noise levels for these aircraft when taxiing from hanger to runway are 100–108 dBA and 83–90 dBA respectively.

2.6. Statistical methods

The outcome of interest for this study is the participants’ hearing thresholds in both ears at eight different frequencies. Socio-demographic characteristics, potential confounders and each hearing threshold were compared across the three exposure groups using a Kruskal–Wallis or Pearson chi-squared test.

A quantile regression model was used to estimate median hearing threshold and determine whether any association exists between F-111 DSRS exposure, the hearing threshold at the eight measured frequencies in both ears, and other possibly confounding variables. Since this approach uses sixteen observations per person, bootstrapped standard errors with 500 replications, clustered on the participant, were used (Horowitz, 1998; Koenker and Bassett, 1978; Narula et al., 1999; Weiss, 1988). All variables of interest were initially included in the model and backwards stepwise
We obtain the approximate probability of a 25 dB or more hearing threshold for noise exposure at this level at these low frequencies. We obtain the approximate probability of a 25 dB or more hearing threshold for an otologically normal male who has experienced 85 dB noise for 10 years by finding $u$ such that $T_{\text{noise}}(u, a, M, f, 10, 85) = 25$.

To estimate the probability of a 25 dB or more hearing threshold for the normal (i.e. non-smoking, non-diabetic, not using anti-depressants or experiencing tinnitus) RAAF male, we used the parsimonious quantile regression model to estimate each hearing threshold percentile, that is for $u = 0.01$ through 0.99. The percentile function was inverted to obtain the cumulative distribution function. This was then smoothed to a curve of the same form as Eq. (2) using two non-linear least-squares models for each age and frequency combination. The upper and lower bounds were smoothed in a similar fashion.

The relative risks of a greater than 25 dB hearing threshold for the normal population were formed by dividing that probability for male RAAF study population by that probability for the normal (i.e. non-smoking, non-diabetic, not using anti-depressants or experiencing tinnitus) RAAF male, we used the parsimonious quantile regression model to estimate each hearing threshold percentile, that is for $u = 0.01$ through 0.99. The percentile function was inverted to obtain the cumulative distribution function. This was then smoothed to a curve of the same form as Eq. (2) using two non-linear least-squares models for each age and frequency combination. The upper and lower bounds were smoothed in a similar fashion.

The relative risks of a greater than 25 dB hearing threshold, and bounds of its 95% confidence interval, were formed by dividing that probability for male RAAF study population by that probability for the normal (i.e. non-smoking, non-diabetic, not using anti-depressants or experiencing tinnitus) RAAF male, we used the parsimonious quantile regression model to estimate each hearing threshold percentile, that is for $u = 0.01$ through 0.99. The percentile function was inverted to obtain the cumulative distribution function. This was then smoothed to a curve of the same form as Eq. (2) using two non-linear least-squares models for each age and frequency combination. The upper and lower bounds were smoothed in a similar fashion.
Table 2
Quantile regression model results for median hearing threshold for male Australian air force personnel (1397 individuals, 22,253 observations).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable detail</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>500 Hz (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000 Hz</td>
<td>-0.26</td>
<td>-5.11, 4.60</td>
<td>0.918</td>
<td></td>
</tr>
<tr>
<td>1500 Hz</td>
<td>-3.22</td>
<td>-8.02, 1.58</td>
<td>0.189</td>
<td></td>
</tr>
<tr>
<td>2000 Hz</td>
<td>-4.3</td>
<td>-9.54, 0.94</td>
<td>0.108</td>
<td></td>
</tr>
<tr>
<td>3000 Hz</td>
<td>-15.47</td>
<td>-20.97, -9.97</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>4000 Hz</td>
<td>-16.83</td>
<td>-22.55, -11.1</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>6000 Hz</td>
<td>-16.37</td>
<td>-22.11, -10.6</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>8000 Hz</td>
<td>-28.89</td>
<td>-35.0, -22.8</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
<td>-1.45</td>
<td>-1.93, -0.97</td>
<td>0.000</td>
</tr>
<tr>
<td>Age-squared/100</td>
<td>Years$^2$/100</td>
<td>1.93</td>
<td>1.40, 2.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Frequency * Age</td>
<td>1000 Hz * age</td>
<td>-0.01</td>
<td>-0.11, 0.09</td>
<td>0.872</td>
</tr>
<tr>
<td></td>
<td>1500 Hz * age</td>
<td>0.07</td>
<td>-0.03, 0.17</td>
<td>0.148</td>
</tr>
<tr>
<td></td>
<td>2000 Hz * age</td>
<td>0.09</td>
<td>-0.02, 0.20</td>
<td>0.127</td>
</tr>
<tr>
<td></td>
<td>3000 Hz * age</td>
<td>0.43</td>
<td>0.31, 0.55</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>4000 Hz * age</td>
<td>0.58</td>
<td>0.45, 0.71</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>6000 Hz * age</td>
<td>0.65</td>
<td>0.52, 0.77</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>8000 Hz * age</td>
<td>0.75</td>
<td>0.61, 0.89</td>
<td>0.000</td>
</tr>
<tr>
<td>Self-reported</td>
<td>tinnitus</td>
<td>Yes</td>
<td>2.77</td>
<td>1.60, 3.93</td>
</tr>
<tr>
<td></td>
<td>4000 Hz * tinnitus</td>
<td>2.86</td>
<td>1.44, 4.28</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>6000 Hz * tinnitus</td>
<td>2.38</td>
<td>0.64, 4.12</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>8000 Hz * tinnitus</td>
<td>1.79</td>
<td>-0.03, 3.62</td>
<td>0.054</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non/ex smoker</td>
<td>Current smoker</td>
<td>1.73</td>
<td>0.44, 3.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosed diabetic</td>
<td>5.88</td>
<td>2.52, 9.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uses anti-depressant meds</td>
<td>4.46</td>
<td>3.09, 5.84</td>
</tr>
</tbody>
</table>

In the quantile regression model, there were no statistically significant differences between the exposed and Amberley (p-value = 0.6) and the exposed and Richmond (p-value = 0.2) comparison groups, therefore for all further analysis all three groups were combined. The interaction between diabetes and the frequency indicators were included initially to allow for the possibility that the effect of diabetes on hearing threshold may vary across frequency, however, the F-test for the interactions was not significant (p-value = 0.1). The parsimonious model is reported in Table 2. The square of age was significant, indicating that the relationship between hearing threshold and age is not simply linear. Age also interacted significantly with some of the frequencies, which means that as we age hearing thresholds at some frequencies are more affected than others. Other than age and frequency, smoking, diabetes, self-reported tinnitus and use of anti-depressant medication were found to have a significant effect on hearing threshold. Study participants with diabetes have median hearing threshold 6 dB (95% CI 3.2, 8.9) greater than those without. Study participants using anti-depressants have median hearing threshold 4.5 dB (95% CI 2.8, 6.2) greater than those who do not. Study participants who smoke have median hearing threshold 1.7 dB (95% CI 0.6, 2.9) greater than those who do not, a clinically small but statistically significant increase. Tinnitus is associated with a 2.8 dB median hearing threshold increase at lower frequencies, and 5.6 dB and 5.1 dB increases at 4 kHz and 6 kHz respectively.

Some coefficients of multivariable models containing interactions can be difficult to interpret directly, thus the display of predictions from such a model is helpful in interpretation. Quantile regression models estimating all percentiles (0.01–0.99) of hearing thresholds as a function of age and frequency were fit. Fig. 1 presents the median, 10th and 90th percentiles estimated thresholds of hearing for non-smoking, non-diabetic males not using anti-depressants or experiencing tinnitus. The median, 10th and 90th percentiles of ISO A screened and ISO B unscreened population data, are also shown. Note that the ISO deciles are curved rather than straight, showing why the age-squared term was significant in the model.

Table 3 shows coefficients estimated by the non-linear regression model of the form of Eq. (1) fit to male ISO Annex B values, and note that the constant terms $c_i(s, f)$ are non-zero as the median hearing threshold for the ISO B unscreened 18 year old is not zero. Fig. 2 presents the estimated median hearing thresholds by age as a function of frequency for: the study population, the ISO A screened population, the ISO A screened with ISO 5.3 adjustments and the ISO B unscreened population. We note an unusual increase

3. Results

Recruitment and participation figures have been reported previously (Attia et al., 2006; Schofield et al., 2006). Briefly, 872 exposed individuals, 1251 Amberley comparisons, and 1264 Richmond comparisons were eligible for inclusion in the General Health and Medical Study, of whom 1538 had a health examination. Hearing was not tested in eight participants and 17 participants did not complete all questions for each instrument. Consequently, totals in each row may vary.

Table 3
Estimated coefficients for hearing thresholds by age for ISO B screened males and females (ISO A screened values included for comparison).

<table>
<thead>
<tr>
<th>Freq. (Hz)</th>
<th>ISO B unscreened</th>
<th>ISO A screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>$\gamma_{upper} = 0.472$, $\gamma_{lower} = 0.332$</td>
<td>$\gamma_{upper} = 0.445$, $\gamma_{lower} = 0.356$</td>
</tr>
<tr>
<td>1000 Hz</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
</tr>
<tr>
<td>2000 Hz</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
</tr>
<tr>
<td>3000 Hz</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
</tr>
<tr>
<td>4000 Hz</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
</tr>
<tr>
<td>6000 Hz</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
<td>$\beta_{upper} = 7.10$, $\beta_{lower} = 5.78$</td>
</tr>
</tbody>
</table>

In the quantile regression model, there were no statistically significant differences between the exposed and Amberley (p-value = 0.6) and the exposed and Richmond (p-value = 0.2) comparison groups, therefore for all further analysis all three groups were combined. The interaction between diabetes and the frequency indicators were included initially to allow for the possibility that the effect of diabetes on hearing threshold may vary across frequency, however, the F-test for the interactions was not significant (p-value = 0.1). The parsimonious model is reported in Table 2. The square of age was significant, indicating that the relationship between hearing threshold and age is not simply linear. Age also interacted significantly with some of the frequencies, which means that as we age hearing thresholds at some frequencies are more affected than others. Other than age and frequency, smoking, diabetes, self-reported tinnitus and use of anti-depressant medication were found to have a significant effect on hearing threshold. Study participants with diabetes have median hearing threshold 6 dB (95% CI 3.2, 8.9) greater than those without. Study participants using anti-depressants have median hearing threshold 4.5 dB (95% CI 2.8, 6.2) greater than those who do not. Study participants who smoke have median hearing threshold 1.7 dB (95% CI 0.6, 2.9) greater than those who do not, a clinically small but statistically significant increase. Tinnitus is associated with a 2.8 dB median hearing threshold increase at lower frequencies, and 5.6 dB and 5.1 dB increases at 4 kHz and 6 kHz respectively.

Some coefficients of multivariable models containing interactions can be difficult to interpret directly, thus the display of predictions from such a model is helpful in interpretation. Quantile regression models estimating all percentiles (0.01–0.99) of hearing thresholds as a function of age and frequency were fit. Fig. 1 presents the median, 10th and 90th percentiles estimated thresholds of hearing for non-smoking, non-diabetic males not using anti-depressants or experiencing tinnitus. The median, 10th and 90th percentiles of ISO A screened and ISO B unscreened population data, are also shown. Note that the ISO deciles are curved rather than straight, showing why the age-squared term was significant in the model.

Table 3 shows coefficients estimated by the non-linear regression model of the form of Eq. (1) fit to male ISO Annex B values, and note that the constant terms $c_i(s, f)$ are non-zero as the median hearing threshold for the ISO B unscreened 18 year old is not zero. Fig. 2 presents the estimated median hearing thresholds by age as a function of frequency for: the study population, the ISO A screened population, the ISO A screened with ISO 5.3 adjustments and the ISO B unscreened population. We note an unusual increase
in the median hearing threshold at 0.5 kHz in all age groups for the ISO B unscreened population data. For the RAAF study population, two observations are warranted: firstly is that the median heading threshold for the RAAF study population at 1 kHz is 10 dB greater than the median of the ISO B unscreened population data. Secondly, also apparent is the notch between 3 and 6 kHz compared to the ISO A screened population data; these frequencies are used as a clinical sign of noise induced hearing loss, therefore it would seem that noise induced hearing loss is apparent in our study population.

The cumulative distribution functions of hearing threshold for ISO A screened, B unscreened, and normal (meaning non-smoking, non-diabetic, does not used anti-depressant medications and has not reported tinnitus) RAAF study population at various ages are shown in Fig. 2, for 6 kHz only. Where the curve for the RAAF study population is to the right of an ISO curve, the probability of a 25 dB or less hearing threshold (at the vertical line) is much lower. By subtracting the probability from one we see that a 25 dB loss or more hearing threshold is much greater for the study population.

The probabilities of a 25 dB threshold or more, the relative risks of a 25 dB or more hearing threshold for the study population compared to: the ISO A screened population, the ISO A screened with ISO 5.3 adjustments and ISO B unscreened population data (International Organisation for Standardisation, 2003). In using this method, we have estimated the relative risk of a 25 dB hearing threshold or more compared to these three datasets while adjusting for other ototoxic/ototraumatic agents (smoking, diabetes, tinnitus and use of anti-depressant medication). This technique makes it possible to estimate the probability and relative risk of any hearing threshold change at various ages and frequencies. To our knowledge such a method of analysis of hearing threshold has not been previously reported.

4. Discussion

This study utilized a large military sample to demonstrate the utility of quantile regression in comparing percentiles of a study population’s hearing thresholds with three datasets: ISO1999 Annex A screened population data, ISO A screened data with ISO 5.3 adjustments and ISO B unscreened population data. Fig. 3c, which shows relative risks of the RAAF study population compared to the ISO A screened data with ISO 5.3 adjustments, show that the probability of a 25 dB or more hearing threshold is highest for young men decreasing with age, with the highest relative risk are at frequencies less than 2 kHz.

4.1. Other risk factors

Using the method described we have been able to quantify the size of the effects of other risk factors on hearing threshold, thus
Table 4

<table>
<thead>
<tr>
<th>Age</th>
<th>Freq.(Hz)</th>
<th>Probability</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RAAF (95% CI)</td>
<td>ISO A scr.</td>
</tr>
<tr>
<td>30</td>
<td>500</td>
<td>0.059 (0.03, 0.10)</td>
<td>0.000</td>
</tr>
<tr>
<td>1000</td>
<td>0.029 (0.01, 0.06)</td>
<td>0.000</td>
<td>0.002</td>
</tr>
<tr>
<td>2000</td>
<td>0.018 (0.01, 0.03)</td>
<td>0.001</td>
<td>0.019</td>
</tr>
<tr>
<td>3000</td>
<td>0.037 (0.02, 0.06)</td>
<td>0.003</td>
<td>0.190</td>
</tr>
<tr>
<td>4000</td>
<td>0.119 (0.08, 0.16)</td>
<td>0.008</td>
<td>0.279</td>
</tr>
<tr>
<td>5000</td>
<td>0.181 (0.14, 0.23)</td>
<td>0.017</td>
<td>0.420</td>
</tr>
<tr>
<td>6000</td>
<td>0.042 (0.02, 0.07)</td>
<td>0.034</td>
<td>1.2 (0.5, 2.1)</td>
</tr>
<tr>
<td>40</td>
<td>500</td>
<td>0.042 (0.03, 0.06)</td>
<td>0.000</td>
</tr>
<tr>
<td>1000</td>
<td>0.029 (0.02, 0.04)</td>
<td>0.000</td>
<td>0.004</td>
</tr>
<tr>
<td>2000</td>
<td>0.043 (0.03, 0.06)</td>
<td>0.007</td>
<td>0.052</td>
</tr>
<tr>
<td>3000</td>
<td>0.136 (0.11, 0.16)</td>
<td>0.029</td>
<td>0.279</td>
</tr>
<tr>
<td>4000</td>
<td>0.256 (0.22, 0.29)</td>
<td>0.072</td>
<td>0.367</td>
</tr>
<tr>
<td>6000</td>
<td>0.340 (0.31, 0.37)</td>
<td>0.111</td>
<td>0.500</td>
</tr>
<tr>
<td>8000</td>
<td>0.160 (0.13, 0.19)</td>
<td>0.174</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>500</td>
<td>0.104 (0.07, 0.14)</td>
<td>0.003</td>
</tr>
<tr>
<td>1000</td>
<td>0.099 (0.07, 0.13)</td>
<td>0.004</td>
<td>0.015</td>
</tr>
<tr>
<td>2000</td>
<td>0.159 (0.12, 0.19)</td>
<td>0.044</td>
<td>0.140</td>
</tr>
<tr>
<td>3000</td>
<td>0.348 (0.31, 0.38)</td>
<td>0.155</td>
<td>0.411</td>
</tr>
<tr>
<td>4000</td>
<td>0.497 (0.46, 0.53)</td>
<td>0.291</td>
<td>0.489</td>
</tr>
<tr>
<td>6000</td>
<td>0.589 (0.57, 0.61)</td>
<td>0.355</td>
<td>0.709</td>
</tr>
<tr>
<td>8000</td>
<td>0.417 (0.38, 0.45)</td>
<td>0.452</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>500</td>
<td>0.324 (0.24, 0.39)</td>
<td>0.017</td>
</tr>
<tr>
<td>1000</td>
<td>0.325 (0.24, 0.39)</td>
<td>0.026</td>
<td>0.048</td>
</tr>
<tr>
<td>2000</td>
<td>0.404 (0.34, 0.46)</td>
<td>0.16</td>
<td>0.292</td>
</tr>
<tr>
<td>3000</td>
<td>0.597 (0.56, 0.63)</td>
<td>0.39</td>
<td>0.600</td>
</tr>
<tr>
<td>4000</td>
<td>0.736 (0.70, 0.77)</td>
<td>0.576</td>
<td>0.693</td>
</tr>
<tr>
<td>6000</td>
<td>0.809 (0.80, 0.82)</td>
<td>0.64</td>
<td>0.851</td>
</tr>
<tr>
<td>8000</td>
<td>0.695 (0.67, 0.72)</td>
<td>0.732</td>
<td></td>
</tr>
</tbody>
</table>

*For denominator probability less than 0.001, relative risk is not calculated.

Fig. 2. Estimated cumulative distribution of hearing threshold for RAAF male personnel, ISO A screened, ISO B unscreened and ISO A screened noise exposed (85 dB for 10 years) at 6 kHz. (a) 30 years of age. (b) 40 years of age. (c) 50 years of age. (d) 60 years of age.
highlighting the importance of using a statistical method which allows the inclusion of such risk factors.

4.1.1. Age
Presbycusis is the gradual hearing loss associated with ageing. The ISO Annex A formulae for deciles of hearing thresholds contain an age-squared term indicating that the relationship between hearing threshold and age is not simply linear; in other words the increase in hearing thresholds from age 20–30 years is not the same as the increase from age 60–70 years (International Organisation for Standardisation, 2003). Thus, in any modelling of hearing threshold an age-squared term should be included and found to be statistically significant. As shown in Table 2, our modelling confirms this supposition.

4.1.2. Tinnitus
Almost half the study participants reported experiencing tinnitus. The mechanisms underlying tinnitus are not completely understood, however some literature suggest this condition is usually accompanied by low-frequency loss (Havia et al., 2002) whilst others suggest high-frequency loss (Martines et al., 2010). Our modelling does show an interaction between frequency and tinnitus; study participants reporting tinnitus had greater hearing thresholds at the higher frequencies (4, 6 and 8 kHz).

4.1.3. Diabetes
Diabetes has been implicated in hearing loss for some time. In 1995, Smith et al. used rates to demonstrate thickening of the basement membrane in capillaries that supply blood to the cochlear (Smith et al., 1995). In 2006, Frisina et al. suggested that the increased porosity of damaged vascular tissues might interfere with hair cell transduction and signal transmission (Frisina et al., 2006). A number of researchers have reported the findings relating to the frequencies where loss occurs in diabetics. Tay et al. (1995) found that diabetics experience higher hearing thresholds primarily at 8 kHz, although Frisina et al. (2006) found the greatest deficits for diabetics at low frequencies. We found no significant difference in the effect of diabetes on hearing thresholds at the various frequencies. An explanation for these varying findings may be that Frisina’s study involved participants aged over 58 years; in this age group presbycusis, which particularly affects high frequencies, is already taking place (Frisina et al., 2006).

4.1.4. Smoking
The effect of smoking on hearing thresholds is relatively well known. Agrawal et al. (2008), Nakanishi et al. (2000) and Nomura et al. (2005) have all found that smokers are at increased risk of hearing loss across all frequencies. This study has confirmed that current smokers have slightly elevated hearing thresholds at all frequencies thereby confirming the importance of including smoking status in hearing studies.

4.1.5. Anxiety, depression and medications
Association between hearing loss and mental health has been reported (Monzani et al., 2008), therefore we included anxiety and depression measured with the Kessler scale (Andrews and Slade, 2001), however it was not statistically significant. Also included in the model was the use of anti-depressant medication as both Vicente-Torres et al. (2003) and Tadros et al. (2007) have reported on the role of serotonin in the cochlea. Our modelling did show a statistically significant effect of using anti-depressants, with hearing thresholds being approximately 5 dB higher for those using these medications. It is not possible to infer the nature of the biological mechanism, so the association may be due a side-effect of...
the medication or it may be that those study participants who have highest hearing thresholds have the worst anxiety/depression and thus take anti-depressant medications.

4.2. Relative risk of increased hearing thresholds

We have shown that the relative risks of a 25 dB or more hearing threshold, compared to the ISO A screened population data are significantly greater than one for all frequencies less than 8 kHz and greatest in younger study participants, possibly because they have exposure to aircraft noise which generally commences at 18–20 years when they enlist in the military. For older study participants, their relative risks compared to the ISO A screened population data are closer to one (although still significantly greater from one), possibly because presbycusis has taken its toll on the ISO A screened population data so their hearing thresholds are “catching up.”

Compared to the ISO B unscreened population data, relative risks are significantly less than one at 3 kHz and above for younger study participants, perhaps because their enlistment screening is “protective” initially. For older study participants, their relative risks are not significantly different to one at these frequencies, possibly because various exposures over time have eroded the “protective” effect of their enlistment screening. For all ages, relative risks are significantly greater than one for 0.5–1 Hz; the frequency with the greatest relative risk is 1 kHz. A similar pattern is observed in the comparison with ISO A screened with Section 5.3 adjustment. Most notable however, are the extremely large relative risks at frequencies less than 2 kHz in all three comparisons and therefore worthy of further discussion.

4.3. Low-frequency hearing thresholds

A number of studies have noted increased hearing thresholds beyond that expected according to an ISO standard population data. One such study by Henselman et al. (1995), in a study of US Military men showing an approximately 5 dB increase in hearing threshold beyond the ISO B unscreened population data, at frequencies between 1 and 4 kHz. The explanation put forward for the observed difference was that the ISO B unscreened population data is out-of-date because it is based on data collected more than 30 years ago. This view has been discussed by a number of other authors (Borchgrevink et al., 2005; Engdahl et al., 2005). Whilst we could intuitively conclude that it is possible that the world has become noisier and more polluted place since the data was collected, thus those with even the best hearing may have somewhat increased hearing thresholds by living in a modern industrialized society Hoffman et al. (2010), in a comparison of the National Health Examination Survey 1 1959–1962 to National Health and Nutrition Examination Survey 1999–2004 found that Americans hear as well or better in the more recent survey. These differences, they concluded may have been due to a number of factors including: changes in standards for ambient noise in audiometry, changes in recruitment which resulted in a larger, contemporary, nationally representative sample, and a higher participation rate which thereby reduced the risk of non-response bias.

Another theory explored is that determining “true” normative age-related hearing thresholds have been difficult to establish as thresholds collected in population studies run the obvious risk of being “contaminated” by hearing loss from factors such as occupational noise, societal noise, and disease/trauma (Borchgrevink et al., 2005). While the usual approach is to collect screened and unscreened population data, Borchgrevnic et al. suggest that screening to eliminate risk factors may implicitly eliminate the poorer part of the normal population, leading to a too good normative hearing threshold for age and consequent overestimation of acquired hearing loss. Conversely, norms based on thresholds from an unscreened population may underestimate the magnitude of an acquired hearing loss and thus leave effects of risk exposure undetected (Borchgrevink et al., 2005). With this supposition in mind, when interpreting the results of this study we do not see an underestimation of risk as would perhaps be expected for the comparison with the ISO B screened population data, rather, in all three comparisons we see elevated relative risks at frequencies less than 2 kHz.

We conclude that the reason for these extraordinarily large relative risks is attributable to the ISO1999 population data and noise loss formula from Section 5.3 do not contain any adjustment for elevated hearing thresholds for less than 2 kHz.

4.4. The ISO1999 standards

1. It is notable that the current version of ISO1999 was created using data collected some 50 years ago. Whilst nutrition and health care have improved greatly during that time, together with a greater understanding of the effect of occupational noise on hearing, exposure to recreational noise has likely increased due to the advent of personal music players with headphones. The vast changes in lifestyle in the last 50 years are a cause of concern for researchers using ISO normative data.

2. The lack of variance information for the ISO data makes it impossible for researchers to ascertain statistically significant differences between their study population and an ISO population. If standard errors were provided it be possible to determine significant differences by looking for non-overlapping confidence intervals.

3. The ISO’s use of the best ear creates a systematic bias in their estimates, leading to smaller hearing thresholds, thus indicating more hearing loss in populations compared to the ISO standard (Dobie, 2006).

4. Change in ISO standards for audiometric testing since 1950 mean that no hearing threshold data collected according to international standards today should be compared to ISO1999 data (Hoffman et al., 2010).

5. Our results highlight apparent inaccuracies in the low-frequency hearing thresholds of ISO1999 A screened and ISO B unscreened. Furthermore, the noise exposure formulae of ISO1999 Section 5.3 do not admit any increase in hearing threshold at 0.5 kHz or 1 kHz if the exposure is not above 93 dB or 89 dB, respectively, regardless of the number of years of exposure. This seems contrary to the notion, made clear by the jute weaver’s study of Taylor in 1965, that while initial hearing loss occurs near 6 kHz, with continued noise exposure over many decades, losses will accumulate at low frequencies as well (Taylor et al., 1965).

4.5. Advantages of our new method

Our new method of analyzing hearing thresholds had a number of advantages:

1. All observations on study participants may be used since the quantile regression model permits the use of bootstrapped standard errors which is appropriate for data correlated within participant. This increases the sample size available for analysis and maximizes the information that can be obtained from the data. Quantile regression is a non-parametric method which allows for the adjustment for multiple known risk factors, unlike more...
4.6. Strengths and weaknesses of the study

Although the medical requirements for entry into the RAAF are stringent and do contain an assessment of hearing, they may not meet the definition of 'otologically normal' according to the ISO-7029, Section 2.1 (International Organisation for Standardisation, 2000). Thus the results of this analysis do not unequivocally demonstrate that the elevated hearing thresholds observed were entirely a result of military service.

5. Conclusions

This paper demonstrates a new method for quantifying the probability of a clinically relevant hearing loss due to a risk factor. Prior to this, researchers were reduced to simplistic methods such as visual comparison of deciles which did not enable the estimation of risk. The new method can use all observed hearing thresholds per study participant, adjust for known confounding factors such as age and gender, and calculate the relative risk of a clinically relevant increase in hearing threshold due to a risk factor of interest.

Acknowledgements

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Appendix A

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- Soozy Smith, PhD, The University of Newcastle Research Associates Ltd, The University of Newcastle, Newcastle NSW.
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Appendix B

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- Dr Deborah Glass, PhD, Department of Epidemiology and Preventive Medicine, Monash University VIC.
- Emeritus Professor Scott Henderson AO, The John Curtin School of Medical Research, The Australian National University ACT.

Appendix C

This journal article has been reviewed by Department of Veterans’ Affairs prior to publication and the views expressed are not necessarily those of the Australian Government.

References


