Objective: Age-related hearing loss is associated with endothelial dysfunction and increased cardiovascular risk, suggesting a vascular etiology. Methylarginines are endogenous nitric oxide synthase inhibitors that cause endothelial dysfunction and increase cardiovascular disease risk. This study is the first to examine the hypothesis that higher serum concentrations of methylarginines are associated with greater hearing loss prevalence.

Study Design/Patients: Cross-sectional audiometric data on hearing levels, and serum methylarginines were collected from a population-based sample of 630 older community-dwelling adults.

Results: Linear regression analysis showed a statistically significant association between higher serum concentrations of asymmetric dimethylarginine (ADMA) and L-arginine and greater degrees of hearing loss for males, particularly over 75 years. Higher body mass index and previous history of stroke were also associated with hearing loss. For females, ADMA concentration was not associated with hearing loss, but higher serum L-arginine concentrations were associated with reduced hearing loss prevalence in older females. Antihypertensive medication use was also associated with reduced hearing loss prevalence. LDL cholesterol and previous myocardial infarction were associated with greater hearing loss.

Conclusions: This study showed a significant association between serum concentrations of ADMA and hearing loss for males, consistent with the association between endothelial dysfunction and hearing loss. The opposite effect of L-arginine on hearing loss in males vs. females might reflect a different role of this precursor towards nitric oxide vs. methylated arginines synthesis. These findings are potentially clinically significant if the association between ADMA and hearing loss is causal, as serum methylarginine levels are modifiable through pharmacotherapeutic/lifestyle interventions.

Hearing loss

With increasing longevity, the prevalence of age-related diseases such as hearing loss is increasing. A common definition of hearing loss is having hearing thresholds greater than 25dbHL, usually at 250Hz, 500Hz, 1,000Hz, 2,000Hz or 4,000 Hz (). Over half of Australia's population aged 60-70 years has hearing loss, increasing to more than 70% of those over 70 years (1) and 80% of people aged over 80 years (2). These statistics are similar for other developed countries (3-5). Hearing loss impacts significantly on quality of life, resulting in poorer physical and mental health outcomes; those with greater hearing loss being affected most (6-7). Hearing loss has been rated the third most problematic condition experienced after chronic pain and restricted physical activity in older Australians (7). In 2006, hearing loss in Australia was estimated to cost almost $12 billion annually (8).

Associations between hearing loss and other co-morbidities

There are numerous reports of associations between hearing loss and other co-morbidities. Significant associations between hearing loss and rate of cognitive decline (9-10), higher rates of cardiovascular disease (11), renal disease (12), poorer erectile function in men (13), and a greater incidence of falls (14) are reported.

Hearing loss, Asymmetric Dimethyl L-arginine (ADMA), and Symmetric Dimethyl L-arginine (SDMA)

Endothelial dysfunction is a physiopathological mechanism causing coronary artery disease and other atherosclerotic diseases (15-16). The methylarginines, Asymmetric dimethylarginine (ADMA) and Symmetric dimethylarginine (SDMA) are well-recognised

markers of endothelial dysfunction and cardiovascular disease. They are elevated in several disease processes, including hypertension, hypercholesterolaemia, diabetes, coronary artery disease, kidney disease, septic shock, and Behcet's disease (17-20). Aging is also associated with endothelial dysfunction (21-22), and hearing loss (1-2). Serum/tissue methylarginine concentrations, known to mediate endothelial dysfunction through inhibition of endothelium-derived nitric oxide synthesis, also increase with aging and other chronic disease states (23-24). Given the rich capillary supply to the stria vascularis in the cochlea, and its sensitivity to disruptions in arterial blood supply, higher methylarginine concentrations may impair endothelial function, and hence blood flow to the cochlea, contributing to hearing loss.

Cardiovascular disease has been associated with hearing loss in multiple studies (11, 25-28). Hearing loss prevalence is 54% greater in people with cardiovascular disease than in the general population (25). An extensive review showed significant negative effects of cardiovascular disease on the auditory system, with potential for improved hearing with improved cardiovascular health (29). Audiometric pattern of hearing loss has even been suggested as a potential predictor of cardiovascular status (30). Vascular endothelial dysfunction may also cause Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) through microvascular impairment, with ISSHL risk increasing with the number of cardiovascular risk factors (31-32). An increased incidence of cardiovascular disease among people with ISSHL has also been reported (33-34), along with a significantly higher incidence of hypertension and diabetes and a greater risk for stroke (35-36). However, no consistent pattern of cardiovascular risk factors has been found (11, 25-26), and some studies report no link between cardiovascular function and hearing loss (3, 37-38).

Given the significant negative effects, identifying potentially modifiable risk factors and markers for hearing loss is a public health priority. Only one study has examined the relationship between hearing loss and serum concentrations of methylarginines; investigating methylarginine-mediated endothelial dysfunction as a causative factor of hearing loss in patients with chronic kidney disease (CKD; 39). Degree of high frequency hearing loss in patients was independently predicted by higher ADMA concentrations, with no association found between hearing loss and age or gender, suggesting the pathogenesis of hearing loss was of a vascular nature. However, there has been no population-based study of the relationship between methylarginines and hearing loss to date.

This study investigated the relationship between serum concentrations of L-arginine and methylarginines and hearing loss in older adults. It was hypothesized that higher serum concentrations of the methylarginines, ADMA and SDMA, would be associated with poorer hearing. This is the first study to examine the association between serum concentrations of methylarginines and hearing. An association between higher serum methylarginine concentrations and hearing loss would be clinically meaningful, as high concentrations of some methylarginines, particularly ADMA, are potentially modifiable through pharmacotherapeutic and lifestyle interventions. Further, higher serum methylarginine concentrations may serve as a biomarker of future hearing loss.

METHODS

Participants

Study participants were from the Hunter Community Study, a population-based cohort study of ageing (40). Participants were community-dwelling people aged 55-85 years, randomly selected from the electoral role, with 9,784 individuals contacted, and 3,253

participating (a response rate of 44.5%). Written informed consent was obtained for all participants, and ethical approval was given by the Newcastle Human Research Ethics Committee (protocol no. H-820-0504a; principal investigator John Attia). A random sample of 630 participants who had audiometric evaluations was selected for serum methylarginine concentration measurement.

Audiological Assessments

Pure tone audiometry was used to measure air and bone conduction thresholds at 500Hz, 1,000Hz, 2,000Hz and 4,000Hz bilaterally using standard audiometric procedures in a sound treated facility. Bone conduction testing was conducted where there was an interaural difference of >10dBHL in air conduction thresholds. Testing was conducted by a clinic nurse, trained by an audiologist, who also examined participants' ears for wax occlusion and collapsed ear canals. Pure tone averages (PTAs; average of hearing thresholds at 500, 1,000 and 2,000Hz) were calculated. A PTA of greater than 25dB hearing level (HL) was defined as hearing loss in accordance with World Health Organization criteria (41). Degree of hearing loss was categorized, based on average PTAs re ANSI-1969 for 500, 1,000 and 2,000Hz (42). Categories were normal (-10-25dbHL), mild (26-40dbHL), moderate (41-70dbHL), severe (71-90dbHL) and profound (91+dbHL). Associations between serum L-arginine, ADMA, L-arginine/ADMA ratio (another proposed marker of atherosclerosis; 43), SDMA concentrations and hearing loss were investigated using both better ear PTA, worse ear PTA and hearing levels at four individual frequencies (for both better and worse ears).

Methylarginine sampling

Blood from participants was collected in EDTA tubes and centrifuged at 4°C and 3,000g for 10 min to separate serum. Serum collected concurrently with audiometric evaluations was stored for 3 years at -80°C prior to analysis. ADMA and SDMA were measured in serum using hydrophilic-interaction liquid chromatography and isotope dilution tandem mass spectrometry (LC-MS/MS), the gold standard for such measurements (44). The intra and inter-assay CVs for ADMA and SDMA were all less than 15%.

Potentially confounding factors

Potentially confounding variables of the association between serum methylarginine concentration and hearing loss were identified from the literature and considered in the analysis (Table 1). All medical co-morbidities were categorized as yes or no.

Statistical analysis

Statistical analyses were conducted using R (45). Demographic and clinical characteristics were compared between participants with normal hearing, mild, and moderate-profound hearing loss (better ear PTA greater than 40db) using an ANOVA test of equality of means.

Multiple linear regressions were conducted, with hearing loss modelled in terms of age, ADMA, SDMA, L-arginine, L-arginine/ADMA ratio and other predictors using regressions of the form:

$$Y_i = \alpha_0 + \alpha_1 \text{age}_i + \alpha_2 X_i + \alpha_3 (\text{age}_i \cdot X_i) + Z_i'\beta + U_i,$$

where Y_i is the outcome (hearing loss (db) in either ear at either the specified frequency or PTA), X_i is one of ADMA, SDMA, L-arginine or the ADMA/L-arginine ratio (each standardised to mean zero and standard deviation one, separately for males and females), and age_i is

included as years over age 55. The vector Z_i contains the selection of demographic and clinical covariates that minimize the Akaike Information Criterion (AIC), which is a bias-corrected estimator of the Kullback-Leibler divergence between the distribution implied by a statistical model and the distribution of the data (46-47).

The regressions were used to estimate the average rate of hearing loss with increasing age and how this rate interacted with ADMA/SDMA/L-arginine/L-arginine-ADMA ratio, while controlling for the covariates in Z_i. The coefficient α_1 gives the average hearing loss (db)/year of age at the mean level of ADMA/SDMA/L-arginine/L-arginine-ADMA ratio (for which $X_i = 0$). The interaction $\left(\text{age}_i \cdot X_i\right)$ allows for the level of ADMA/SDMA/L-arginine/L-arginine-ADMA ratio to vary the average rate of hearing loss. Generally, the average rate of hearing loss/year of age was $\alpha_1 + \alpha_3 X_i$, so that above/below average levels of ADMA/SDMA/L-arginine/L-arginine-ADMA ratio may increase or decrease the rate of hearing loss depending on the sign and significance of α_3.

Similarly, the marginal effect of an additional 1 S.D. of X_i on hearing loss may depend on age_i, and is given by $\alpha_2 + \alpha_3 \text{age}_i$. Thus α_2 is the marginal effect of X_i on hearing loss for 55 year-olds, and this marginal effect may increase or decrease with age depending on the sign and significance of α_3.

The intercept α_0 is the average hearing loss for those where the explanatory variables are all equal to zero. Since overall average hearing losses are already given in Table 2a, interpretation of the regression results focusses on the marginal effects above.

RESULTS

Demographics

Table 1 lists the biological, lifestyle and sociodemographic factors measured, and Table 2a describes hearing acuity. Hearing loss prevalence was 51.7% using better ear PTA, and 70% using worse ear PTA. Using better ear PTA, 48% of participants had mild, 3.5% moderate, and 0.2% had severe or greater hearing loss respectively. Using worse ear PTA, 60% had mild, 8.2% moderate, and 1.8% had a severe loss or worse. Average magnitudes of hearing loss were 23.59 dbHL (better ear) PTA and 28.78 dbHL (worse ear), placing in context the marginal effect sizes reported for the linear regressions.

Table 2b shows hearing loss prevalence of (better ear PTA) according to age and gender. This increased with age; more women than men had mild hearing loss, more men than women had moderate hearing loss, and only women had severe hearing loss. Table 3a shows demographic and clinical characteristics for the sample by extent of hearing loss.

Males - Worse Ear

Multiple linear regression analysis showed that increased serum ADMA concentration was associated with increased rates of hearing loss in the worse ear for males (Table 4b). At average serum concentrations of ADMA (i.e. at $\text{ADMA}_i = 0$) the estimated average rate of hearing loss was 0.709dbHL/year of age. This rate increased with higher levels of ADMA; for example, with ADMA levels 1 S.D. above average, the estimated rate of hearing loss became $0.709 + 0.301 \times 1 = 1.01$dbHL per year. An increase in the rate of hearing loss of 1.01 – 0.709 = 0.301 dbHL/year, sustained over 20 years, implies an overall additional hearing loss of 6.02dbHL. To put this into context, it is approximately 20% of the overall average worse ear hearing loss of 28.78 dbHL.

The marginal effect of additional ADMA is summarised in Figure 1. An additional 1 S.D. of ADMA resulted in significantly higher average hearing loss (PTA) for males above age approximately 75 years (i.e. the approximate age from which the 95% confidence interval excludes zero). The effect size for an 85 year-old was approximately 5dbHL.

Figure 2 shows the variation in the rate of PTA hearing loss per extra year of age across the range of observed ADMA concentrations. At low ADMA concentrations (less than 1 S.D. below the mean), the rate of hearing loss per year was statistically insignificant, but exceeded 1db per year once ADMA concentrations exceeded 2 S.D. above average. These effects were also observed at 500Hz, 1,000Hz and 2,000Hz, but not at 4,000Hz.

Higher BMI was also associated with significantly greater hearing loss, particularly at 500Hz, where an extra point of BMI, holding all else constant, was associated with increased average hearing loss of approximately 0.6dbHL. Holding all else constant, a history of stroke was also associated with hearing loss at higher frequencies (2,000Hz and 4,000Hz), and with less hearing loss, however only 9 males had a history of stroke.

There was no association between increased concentration of serum SDMA or L-arginine/ADMA ratio and hearing loss in the worse ear (Table 3).

Males - Better Ear

Increased serum ADMA concentration was associated with increased rates of hearing loss in the better ear for males (Table 4b). Higher ADMA concentrations were significantly associated with greater hearing loss in the better ear at 1,000Hz, 2,000Hz and 4,000Hz, but not at 500Hz. The interpretations are qualitatively similar to those for the worse ear, but with lower levels of hearing loss. Estimated better ear PTA hearing loss was 0.6dbHL per year at average concentrations of ADMA, rising to 1.0dbHL per year with ADMA concentration 2 S.D. above average.

Increased serum L-arginine concentrations were also significantly associated with greater levels of hearing loss over age 70. Further, increased concentrations of serum L-arginine were associated with increased rates of hearing loss at 1,000Hz and 2,000Hz.

There was no association between increased concentrations of serum SDMA or L-arginine/ADMA ratio and hearing loss in the better ear.

Females - Worse Ear

In contrast, there was a trend towards a significant association between higher serum ADMA concentrations and lower levels of hearing loss in the worse ear for females

(Table 4c). Higher serum L-arginine concentrations were also associated with less hearing loss in the worse ear (Table 4c, Figure 3). Figure 3 shows the profile of the estimated rate of hearing loss/year of age from age 55 across the observed variation in serum L-arginine concentrations. The estimated rate of hearing loss for females with average levels of blood serum L-arginine was 1.158 dbHL per year. For example, L-arginine concentration 1 S.D. above the mean was associated with a $1.158+(-0.260) \times 1 = 0.898$ dbHL per year rate of hearing loss. Estimated rates ranged from approximately 1.7db/year at L-arginine concentration 2 S.D. below average to approximately 0.7 dbHL/year at L-arginine concentration 1 S.D. above average. Sustained across 20 years, a difference of 1 dbHL/year in hearing loss is could be substantial (relative to the mean worse ear PTA overall hearing loss for females of 29.1 dbHL, for example).

The estimated marginal effects of an additional 1 S.D. of L-arginine were calculated from the linear regression as $1.425 - 0.260\ \text{age}_i$. Until approximately age 70, increased serum L-arginine concentration was not significantly associated with degree of hearing loss, but was over age 70 years.

The linear regression models for individual hearing frequencies imply that the significant effect of increased L-arginine concentrations on average hearing loss was only at the lower frequencies (only equations for 500Hz and 1,000Hz had significant L-arginine/age interaction terms). There was no evidence that rate of hearing loss varied across frequencies; the coefficients on age ranged between 1.0-1.2dbHL.

The use of antihypertensive medication was also significantly associated with reduced average level of hearing loss for females, with a marginal effect size ranging from approximately 4.7dbHL at 500Hz to 7.0dbHL at 4,000Hz (Table 4c).

There was no association between increased concentrations of serum SDMA or L-arginine-ADMA ratio and hearing loss in the worse ear for females.

Females - Better Ear

Evidence of a trend between higher concentrations of serum L-arginine and reduced rate of hearing loss in the better ear was weak (Table 4d), with a statistically significant effect only at 1000Hz.

There was no statistically significant association between increased concentrations of serum ADMA, SDMA or L-arginine-ADMA ratio and hearing loss in the better ear (Table 4d).

DISCUSSION

This study is the first to examine the relationship between the cardiovascular risk factors, serum ADMA and SDMA, and serum L-arginine, and hearing in any population. There was a significant positive association between serum concentrations of ADMA and increased hearing loss in males, particularly over age 75 years. Higher serum L-arginine concentrations were also associated with increased hearing loss at 1 and 2kHz in males aged over 70 years. Given that endothelial dysfunction and cardiovascular disease are strongly associated with hearing loss (11, 32, 35-36), this finding suggests that ADMA may inhibit endothelium-derived nitric oxide synthesis and vasodilatation and impair blood flow to the inner ear, resulting in hearing loss. Similar findings for CKD patients have been reported (39). These findings are potentially clinically significant because high serum methylarginine concentrations are modifiable through pharmacotherapeutic and lifestyle interventions (48-50). If this association is causal, testing for high serum methylarginine levels and treating accordingly may delay the onset of hearing loss, at least for males. Elevated serum concentrations of ADMA have consistently been demonstrated in individuals with traditional vascular risk factors (51-52) and those with cardiovascular disease (20, 53-55) and independently predict cerebrovascular disease and dementia (55-57). Higher serum methylarginine concentrations have also been associated with increased mortality in numerous longitudinal studies involving healthy (54, 58) and patient populations (20, 53, 55).

Higher BMI was also associated with increased hearing loss in males. The literature reports a greater likelihood of endothelial dysfunction and accompanying vascular disease in overweight people (59-60). A history of stroke was also found to be associated with decreased hearing loss for males in this study, probably due to the positive effects of antihypertensive medication (61) on endothelial function (62).

For females, however, there was no significant effect of ADMA found. Instead, higher serum L-arginine concentrations were associated with less hearing loss, particularly for low frequency hearing in females aged over 70 years. The use of antihypertensive medication, having high LDL cholesterol, and previous myocardial infarction were also significantly associated with hearing loss for females.

The opposite effects of serum L-arginine on hearing observed in males and females (higher L-arginine with less hearing loss in females and greater hearing loss in males) in this study suggest that the relationship between hearing loss, L-arginine, nitric oxide synthesis and endothelial function is complex and possibly gender-dependent. Given that gender differences exist in the L-arginine-nitric oxide pathway within the renal and cardiovascular systems (63-64), the findings of this study may represent another dimorphism in the pathogenesis of hearing loss in males and females. L-arginine is also the natural precursor of the methylated arginines ADMA and SDMA (65), therefore, the opposite effects of L-arginine in older males and females might reflect a gender-specific balance between being a precursor of nitric oxide synthesis by nitric oxide synthases or being a substrate for methylation by protein arginine methyltransferases (PRMTs), with consequent synthesis of methylated arginines. Further research may confirm this finding and explore the mechanism by which L-arginine affects hearing.

No significant associations between L-arginine/ADMA ratio or serum SDMA concentrations and hearing loss were found. L-arginine/ADMA ratio has been proposed as a marker of atherosclerosis in previous studies (43), based on the role of L-arginine as a substrate for nitric oxide synthesis. However, L-arginine is also the direct precursor of methylated arginines synthesis by PRMTs (65), therefore, measuring the L-arginine/ADMA ratio may not reflect a balance between nitric oxide synthesis and inhibition because of its dual role. There is increasing evidence that SDMA might indirectly modulate nitric oxide synthesis and adversely affect cardiovascular homeostasis (66). Although SDMA was not significantly associated with hearing loss in our population, further studies including a larger number of subjects with higher SDMA concentrations (e.g. CKD) are warranted.

In considering these results, it is important to consider how representative these findings on hearing loss are. Comparing hearing loss incidence between different cohorts is often problematic, given the effects of different sample characteristics and methodologies. There is no standard definition of hearing loss, or standard categories of hearing loss, and different testing methodologies yield different results. Further modifying factors include the ear used to measure hearing loss (better or worse), and the frequencies used. Prevalence estimates range widely from 30-83%, depending on the definitions of hearing loss used (67-68). Prevalence in this study falls within the reported ranges, although closer to the higher end (70-71). However, the majority of participants in this study had only a mild hearing loss (<40dBHL; 48% better ear PTA; 60% worse ear PTA). Most studies report on prevalence of hearing loss, but not on severity of loss, therefore the results of this study can only be compared with those of two epidemiological studies. The Epidemiology of Hearing Loss study reported a mild loss in the worse ear for the majority of participants (58.15%; 70). The Blue Mountains Eye study showed 39.1% of participants had a mild loss in

the better ear, with only a further 15.6% having greater degrees of loss (72). In the current study, 48% of participants had a mild hearing loss in their better ear, comparable with the Blue Mountains Eye study finding, and 60% of participants had a mild loss in the worse ear, again comparable with results of the Beaver Dam study. Although the prevalence and severity of hearing loss for this cohort are comparable, the fact that hearing impairment was mostly only mild (93% in the better ear and 86% in the worse ear) could have limited the sensitivity of our analyses.

This study has a number of strengths. It was conducted in a relatively large population-based sample of community-dwelling older adults, serum L-arginine, ADMA, and SDMA were all measured using the gold standard for methylarginine measurement, and hearing loss was measured objectively using a validated gold standard.

Study limitations include its cross-sectional nature, which precluded the investigation of a causal relationship between methylarginines and hearing loss. Further, similar to most methylarginine studies, the measurement of ADMA and SDMA from blood does not necessarily reflect intracellular concentrations of these compounds.

CONCLUSION

This study showed that increased serum concentrations of ADMA and serum L-arginine were associated with increased hearing loss for older males, suggesting that endothelial dysfunction may mediate this association. This finding is potentially clinically significant, given serum methylargine concentrations are modifiable through pharmacotherapeutic and lifestyle interventions. Serum ADMA concentrations were not associated with hearing for females. Higher serum L-arginine concentrations were associated with less hearing loss over age 70 years in females, which may reflect gender

differences in the role of L-arginine in hearing loss. Further epidemiologic studies are required to confirm these findings, including populations with more severe hearing loss, and investigating whether the association between serum methylarginine concentrations and hearing loss is causal.

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Figure Legends

Figure 1.

Estimated marginal effect sizes on PTA worse ear hearing loss (dBHL) in males of an increase of 1 S.D. of serum ADMA concentration, calculated from the regression results in Table 3. The effect sizes are calculated for each age between 55 and 85 years, with 95% confidence intervals shown by the dashed lines. Confidence intervals that exclude zero indicate effect sizes that are statistically significant at the 5% level.

Figure 2.

Estimated marginal effect sizes on PTA worse ear hearing loss (dBHL) in males of an increase of one year of age, calculated from the regression results in Table 3. The effect sizes are calculated across the range of observed serum ADMA concentrations, with 95% confidence intervals shown by the dashed lines.

Figure 3.

Estimated marginal effect sizes on PTA worse ear hearing loss (dBHL) in females of an increase of one year of age, calculated from the regression results in Table 3. The effect sizes are calculated across the range of observed serum L-arginine concentrations, with 95% confidence intervals shown by the dashed lines.

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