Sex-Related Cochlear Impairment in Cigarette Smokers

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Background: A number of studies have documented the influence of cigarette smoking on hearing. However, the association between sex and hearing impairment in smokers as measured by otoacoustic emissions (OAEs) has not been clearly established. The aim of this study was to analyze sex-specific effects of smoking on hearing via conventional and ultra-high-frequency pure tone audiometry (PTA), and OAEs, specifically spontaneous OAEs, click-evoked OAEs, and distortion-product OAEs.

Material/Methods: The study included 84 healthy volunteers aged 25–45 years (mean 34), among them 46 women (25 non-smokers and 21 smokers) and 38 men (16 non-smokers and 22 smokers). The protocol of the study included otorhinolaryngologic and laryngological oncology in Zabrze, Medical University of Silesia, Katowice, Poland

Results: Smokers and non-smokers did not differ significantly in terms of their hearing thresholds assessed with tone audiometry. Male smokers presented with significantly lower levels of CEAOEs and DPOAEs than both male non-smokers and female smokers.

Conclusions: Smoking does not modulate a hearing threshold determined with PTA at low, moderate, and ultra-high frequencies, but causes a significant decrease in OAE levels. This effect was observed only in males, which implies that they are more susceptible to smoking-induced hearing impairment. Sex-specific differences in otoacoustic emissions level may reflect influences of genetic, hormonal, behavioral, and/or environmental factors.

MeSH Keywords: Hearing Loss • Otoacoustic Emissions, Spontaneous • Smoking

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Background

Our knowledge regarding the harmful effects of tobacco smoke on hearing is still limited. Smoking was shown to result in vascular lesions and changes in some characteristics of the blood, leading to hypoxia-induced injury of various tissues, including the organ of hearing [1–3]. Researchers from the University of Washington in Seattle (United States) and University of Melbourne (Australia) analyzed the 1980–2012 data on the prevalence of cigarette smoking in 187 countries. They showed that the number of smokers older than 15 years of age increased from 721 million in 1980 to roughly one billion (967 million) in 2012. Also, the total number of smoked cigarettes increased, from 4.96 billion to 6.25 billion annually. Currently, the population of male and female smokers is estimated at 31% and 6.2% worldwide, respectively; 30 years earlier, these were 41% and 10%, respectively. According to the WHO data from 2011, the number of adult smokers in Poland is 28% lower than in 1995. Nevertheless, 27.2% of adults in Poland smoke and mean cigarette consumption is 15.4 per day. The percentages of male and female smokers in Poland are estimated at 33.6% and 20.5% of the adult population, respectively. The vast majority of Polish smokers are individuals between 45 and 59 years of age (36%), with 62.5% having primary or vocational education and 43% currently unemployed [4].

Exposure to harmful components of cigarette smoke leads to disorders of lipid metabolism and vascular endothelial dysfunction, which is reflected by enhanced atherosclerosis and increase in blood viscosity [1,2,5,6]. Carbon oxide present in tobacco smoke is a substrate for carboxyhemoglobin synthesis. Despite markedly higher affinity than hemoglobin, carboxyhemoglobin delivers significantly less oxygen to the tissues [7–10]. The vasoconstrictive effect of nicotine results in an impairment of tissue perfusion, which may be associated with cellular dysfunction in the case of chronic exposure to tobacco smoke [1,2,5,9]. According to one hypothesis, the harmful effects of tobacco smoke on hearing are associated with the toxic dysfunction of nicotinic acetylcholine receptors (nAChRs), a vital component of the hearing pathway [11,12]. Moreover, the toxic components of cigarette smoke were shown to impair the redox system, which was reflected by enhanced tissue hypoxia and injury, inter alia impairment of the active mechanisms of the outer hair cells (OHCs) of the cochlea [13–15]. Measurement of OAEs is the only available non-invasive test for selective analysis of the OHC activity, enabling simple, objective, and highly sensitive functional examination of the hearing organ [16,17].

The aim of this study was to analyze the sex-specific effect of cigarette smoking on the results of subjective and objective examination of hearing, namely ultra-high frequency PTA, spontaneous otoacoustic emission (SOAE), and CEOAE and DPOAE levels.

Material and Methods

The study included 84 healthy volunteers aged between 25 and 45 years (mean 34 years), among them 41 non-smokers (mean age 33.3 years) and 43 smokers (mean age 34.7 years). The sample comprised 46 women (25 non-smokers and 21 smokers) and 38 men (16 non-smokers and 22 smokers). None of the participants had a history of audiological impairment. The group of smokers included the individuals who smoked at least 15 cigarettes per day for at least 7 years. The group of non-smokers included only the individuals who had never smoked. The exclusion criteria of the study were: abnormal result of otoscopic examination, history of ear problems, conductive hearing impairment, exposure to noise and ototoxic factors, disorders of cholesterol metabolism, arterial hypertension, chronic metabolic disorders (such as diabetes mellitus or kidney diseases), head injuries associated with the loss of consciousness, family history of genetic-related hearing impairment, disorders of the central nervous system, other acute or chronic systemic conditions, and abnormal body mass index (BMI). Moreover, none of the women participating in this study used hormonal preparations. All the participants were white. Mean body height of the study subjects was 172 cm (range 155–190 cm).

The protocol of the study was approved by the Local Bioethics Committee at the Medical University of Silesia (decision no. KNW/0022/KBI/28/09). All the experiments were conducted in accordance with the Declaration of Helsinki (revision 6, 2008) regarding the principles of human experimentation. Written informed consents were obtained from all the participants prior to any procedure included in the study protocol.

The protocol of the study included history-taking, otoscopic examination, tympanometry, PTA, and the evaluation of different types of OAEs.

PTA included air-conduction audiometry at 250–8 000 Hz, bone-conduction audiometry at 250–400 Hz, and ultra-high-frequency PTA at 8 000–20 000 Hz. PTA was performed in a sound-treated room, using an AC-40 Interacoustics Audiometer.

All otoacoustic emission tests (CEOAEs, DPOAEs, and SOAEs) were conducted with an Echoprobe ILO292 analyzer system, version 6.0 (Otodynamics). Otoacoustic emissions were performed separately for each ear. Prior to the test, the software automatically checked the resonance of the external ear canal and the probe sealing. CEOAEs were recorded in a nonlinear mode with 80-millisecond clicks presented at 85±3 dB pSPL and at a 50 per second rate. Recordings were time-windowed from 2.5 to 20 milliseconds. The responses to a total of 260 sets of clicks were averaged above the noise rejection level of 45 dB. The ILO292 system averages into 2 alternate buffers:
A and B. The signal is estimated from the \((A+B)/2\) waveform, and the noise from the A-B difference waveform. The reproducibility is defined as the zero-lag correlation coefficient between the A and B buffers. CEOAEs were measured within the range of 1.0–5.0 kHz; the overall CEOAE response was analyzed.

DPOAEs were measured using a 2-channel probe using the same ILO292 analyzer system. For CEOAEs, a soft adapter was used to provide precise adaptation of the probe to the wall of the external ear canal. The otoacoustic emissions evoked by 2 tonal signals of different frequencies \((f_1, f_2)\) in a constant relation \((f_1/f_2 = 1.22)\) were recorded. The levels of primary tones were different: \(L_1 = 71\) dB SPL and \(L_2 = 60\) dB SPL (according to Neely’s and Gorg’s formula: \(L_1 = 44 + 0.45 \times L_2\)); the tones were delivered at a constant frequency ratio \(f_1/f_2 = 1.22\). The DP-grams for \(2f_1-f_2\) were collected for the \(f_1\) frequencies of 842 Hz to 7996 Hz with the resolution of 4 points per octave. Subsequently, DPOAEs were tested at the following intensities of primary stimuli, and the distortion \(2f_1-f_2\) was analyzed. DPOAEs were tested as a function of DP-gram and the input/output function at \(L_1 = 40\) dB SPL, 45 dB SPL, 50 dB SPL, 55 dB SPL, 60 dB SPL, 65 dB SPL, and 70 dB SPL. The input/output function was analyzed at 1000 Hz, 1500 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 5000 Hz, and 6000 Hz.

The CEOAEs were considered present at Resp ≥3 dB SPL and Repro >75%, whereas DPOAEs whenever the signal-to-noise ratio (S/N) was higher than at 3 dB, irrespective of frequency. Similar criteria were implemented in the case of SOAEs.

Statistical analysis was carried out with a Statistica 8.0 PL package (StatSoft, United States). Normal distribution of the analyzed variables was verified with the Shapiro-Wilk test. The Student t-test and the Mann-Whitney U-test were used for the intergroup comparisons of normally and non-normally distributed ranked variables, respectively (non-smokers vs. smokers, female non-smokers vs. male non-smokers, female non-smokers vs. female smokers, male non-smokers vs. male smokers, and female smokers vs. male smokers). The Bonferroni correction for the repeated measurements was applied.

We did not conduct an ANOVA (except from CEOAE – Repro, Resp, Noise) due to the characteristics of data distribution (lack of normality) and their specific characteristic (the measurements were taken at 5-unit intervals, up to a maximum value). Parametric tests could be used solely for DPOAE-noise.

The results of PTA and ultra-high frequency PTA were recorded to the nearest 5th unit of the interval scale. Due to lack of normal distribution, the Mann-Whitney U-test was used with Bonferroni correction for repeated measurements.

Since the results for DPOAE were not distributed normally, the Mann-Whitney U-test was used with Bonferroni correction for repeated measurements. The only variable with normal distribution was DPOAE (Noise); therefore, the Student t-test was conducted with Bonferroni correction for repeated measurements.

In the case of CEOAE, Resp (dB), Repro (%), and Noise (dB) variables were distributed normally; therefore, the Student t-test was used to compare them. Stab (%) was the only variable without a normal distribution; therefore, the Mann-Whitney U-test was conducted. No Bonferroni correction was used owing to lack of repeated measurements.

The statistical characteristics of the analyzed variables are presented as means and their standard deviations (SD). The threshold of statistical significance for all the tests was set at \(p < 0.05\).

## Results

### Hearing threshold assessed with PTA

Smokers and non-smokers did not differ significantly in terms of their hearing thresholds at 250-20 000 Hz. Nevertheless, the smokers presented with slightly higher hearing thresholds at all the frequencies examined (\(p > 0.05\): PTA thresholds at 250–8 000 (Figures 1–5) and PTA thresholds at ultra-high frequencies (Figures 6–10).

### Click-evoked otoacoustic emissions

The levels of CEOAEs is smokers were always lower than in non-smokers, but most of these differences did not prove significant on statistical analysis. The only statistically significant differences in the overall CEOAE levels were found when the results of male smokers were compared with those of male non-smokers (\(p = 0.026\)) and female smokers (\(p = 0.001\)) (Tables 1–5). This suggests that, in contrast to smoking women, male smokers are at increased risk of functional OHC impairment.

### Distortion-product otoacoustic emissions (DP-gram function)

The analyzed groups did not differ significantly in terms of their DPOAE levels at various frequencies, both in SNR analysis and when the overall response level was considered. The only exception pertained to the level of DPOAEs at \(f_1 = 1685\) Hz, which was significantly lower in male smokers than in male non-smokers. All the results are presented in Tables 6–10. Irrespective of the testing conditions, no significant intergroup differences were found with regards to the background noise level.
Active and passive mechanisms of the cochlea (I/O function of DPOAEs)

Aside from significant differences between smokers and non-smokers overall, we also found significant differences between male smokers and male non-smokers, as well as between male and female smokers. This suggests that smoking may impair the cochlear mechanisms, but predominantly in males. Irrespective of the testing conditions, no significant intergroup differences were found with regards to the background noise level.

Smokers presented with significantly lower levels of DPOAEs than non-smokers at the following frequencies ($f_2$) and stimulus intensities ($L_2$): 1000 Hz +60 dB SPL and 45 dB SPL, 1500 Hz +70 dB SPL, 65 dB SPL, 60 dB SPL and 40 dB SPL, 2000 Hz +80 dB SPL, and 12.5 kHz +110 dB SPL.
Figure 7. PTA thresholds at high frequencies in male smokers (squares) and male non-smokers (circles).

Figure 9. PTA thresholds at high frequencies in male smokers (squares) and female smokers (circles).

Figure 8. PTA thresholds at high frequencies in female smokers (squares) and female non-smokers (circles).

Figure 10. PTA thresholds at high frequencies in male non-smokers (squares) and female non-smokers (circles).

Table 1. CEOAE levels in smokers and non-smokers.

| Parameter | Smokers | | | Non-smokers | | | | p |
|-----------|---------|--------------|----------|--------------|----------|----------|----------|---|
|           | n (ears) | Mean         | SD       | n (ears) | Mean         | SD       | | |
| Resp dB   | 81       | 10.74        | 4.46     | 75       | 10.88        | 3.63     | | 0.833 |
| Repro %   | 81       | 92.59        | 6.11     | 75       | 92.56        | 6.76     | | 0.975 |
| Noise dB  | 81       | -1.80        | 3.08     | 75       | -1.65        | 3.51     | | 0.791 |
| Stab %    | 81       | 99.74        | 0.95     | 75       | 99.57        | 2.69     | | 0.871 |

Table 2. CEOAE levels in male smokers and female smokers.

| Parameter | Male smokers | | | Female smokers | | | | p |
|-----------|--------------|--------------|----------|---------------|----------|----------|----------|---|
|           | n (ears) | Mean         | SD       | n (ears) | Mean         | SD       | | |
| Resp dB   | 39       | 9.13         | 3.55     | 42       | 12.24        | 4.73     | | 0.001 |
| Repro %   | 39       | 90.74        | 6.82     | 42       | 94.31        | 4.84     | | 0.009 |
| Noise dB  | 39       | -1.80        | 2.92     | 42       | -1.79        | 3.25     | | 0.983 |
| Stab %    | 39       | 99.85        | 0.37     | 42       | 99.64        | 1.27     | | 0.760 |
and 45 dB SPL. These findings suggest that smoking impairs both active and passive mechanisms of the cochlea, especially at lower and moderate frequencies (1–3 kHz).

Compared to male non-smokers, male smokers presented with significantly lower DPOAE levels in an I/O function at the following frequencies (f2) and stimulus intensities (L2): 1000 Hz +60 dB SPL, 55 dB SPL, and 45 dB SPL. In contrast, male and female non-smokers did not differ significantly in terms of their DPOAE levels in an I/O function. All the results are presented in Tables 11–15.

Altogether, the aforementioned data suggest that smoking impairs the OHC function in men, but not in women.

Spontaneous otoacoustic emissions

The results of SOAE analysis were consistent with the above-mentioned data on DPOAE levels in an I/O function. Male smokers were at greater risk of toxic OHC impairment than female smokers. SOAEs were observed in 4.3% and 25% of male smokers and female smokers, respectively.

| Parameter | Male non-smokers | Female non-smokers | p   |
|-----------|------------------|--------------------|-----|
|           | Mean             | SD                 | Mean | SD     |       |
| Resp dB   | 29               | 11.21              | 3.86 | 10.67  | 3.51  | 0.541 |
| Repro %   | 29               | 93.90              | 5.96 | 91.72  | 7.16  | 0.159 |
| Noise dB  | 29               | –2.17              | 3.71 | –1.33  | 3.39  | 0.329 |
| Stab %    | 29               | 99.76              | 0.44 | 99.46  | 3.43  | 0.378 |

Table 3. CEOAE levels in male non-smokers and female non-smokers.

| Parameter | Male smokers | Male non-smokers | p   |
|-----------|--------------|------------------|-----|
|           | Mean         | SD               | Mean | SD     |       |
| Resp dB   | 39           | 9.13             | 3.55 | 29     | 11.21 | 3.86  | 0.026 |
| Repro %   | 39           | 90.74            | 6.82 | 29     | 93.90 | 5.96  | 0.047 |
| Noise dB  | 39           | –1.80            | 2.92 | 29     | –2.17 | 3.71  | 0.662 |
| Stab %    | 39           | 99.85            | 0.37 | 29     | 99.76 | 0.44  | 0.372 |

Table 4. CEOAE levels in male smokers and male non-smokers.

| Parameter | Female smokers | Female non-smokers | p   |
|-----------|----------------|--------------------|-----|
|           | Mean           | SD                 | Mean | SD     |       |
| Resp dB   | 42             | 12.24              | 4.73 | 46     | 10.67 | 3.51  | 0.083 |
| Repro %   | 42             | 94.31              | 4.84 | 46     | 91.72 | 7.16  | 0.048 |
| Noise dB  | 42             | –1.79              | 3.25 | 46     | –1.33 | 3.39  | 0.520 |
| Stab %    | 42             | 99.64              | 1.27 | 46     | 99.46 | 3.43  | 0.351 |

Table 5. CEOAE levels in female smokers and female non-smokers.
Table 6. DPOAE levels in smokers and non-smokers.

| Frequency | Smokers Mean | SNR | Non-smokers Mean | SNR | p | p noise | p SNR |
|-----------|--------------|-----|------------------|-----|---|---------|-------|
| 842 Hz    | 4.19         | 3.83| 5.94             | 6.10| .441| 8.27    | 5.49  |
| 1184 Hz   | 6.77         | 3.61| 12.88            | 6.97| 6.91| 6.05    | 7.02  |
| 1416 Hz   | 7.76         | 3.80| 14.34            | 8.89| 7.35| 3.45    | 16.06 |
| 1685 Hz   | 8.28         | 6.46| 9.47             | 6.04| 7.67| 2.76    | 17.14 |
| 2002 Hz   | 7.26         | 5.77| 7.75             | 7.23| 9.37| 2.26    | 17.12 |
| 2380 Hz   | 6.10         | 7.05| 7.18             | 6.23| 9.98| 2.52    | 17.16 |
| 2832 Hz   | 4.83         | 8.15| 7.45             | 6.96| 10.24| 1.86   | 17.69 |
| 4004 Hz   | 9.11         | 7.92| 10.30            | 6.42| 9.87| 1.76    | 20.09 |
| 4761 Hz   | 10.11        | 7.91| 11.39            | 7.09| 9.43| 2.21    | 20.83 |
| 5652 Hz   | 6.87         | 6.16| 7.72             | 8.66| 10.12| 2.78   | 17.26 |
| 6726 Hz   | -0.62        | 9.68| 0.75             | 10.58| 11.39| 2.60   | 12.14 |
| 7996 Hz   | -15.35       | 12.55| 12.17            | 13.10| 13.92| 2.48   | 11.53 |

Table 7. DPOAE levels in male smokers and female smokers.

| Frequency | Male smokers Mean | SNR | Female smokers Mean | SNR | p | p noise | p SNR |
|-----------|------------------|-----|---------------------|-----|---|---------|-------|
| 842 Hz    | 2.93             | 5.00| 3.44               | 4.99| .354| 1.00    | 0.309 |
| 1001 Hz   | 2.89             | 5.40| 6.57               | 6.06| .609| 1.00    | 0.278 |
| 1184 Hz   | 5.51             | 7.64| 8.53               | 11.52| 6.06| .652    | 1.00  |
| 1416 Hz   | 5.82             | 6.74| 7.50               | 9.43| 2.21| 1.08    | 1.00  |
| 1685 Hz   | 6.73             | 5.93| 6.96               | 7.94| 2.79| 1.00    | 0.515 |
| 2002 Hz   | 6.14             | 5.96| 5.84               | 9.19| 2.74| 1.00    | 0.529 |
| 2380 Hz   | 6.8             | 6.02| 7.25               | 6.30| 2.62| 1.00    | 0.672 |
| 2832 Hz   | 4.05             | 5.64| 8.54               | 10.41| 2.10| 1.00    | 0.992 |
| 3369 Hz   | 6.53             | 8.10| 6.74               | 10.09| 2.50| 1.00    | 0.996 |
| 4004 Hz   | 7.84             | 6.71| 9.98               | 2.27| 20.39| 6.25   | 0.882 |
| 4761 Hz   | 8.55             | 9.01| 7.36               | 9.28| 1.91| 21.34   | 6.30  |
| 5652 Hz   | 5.98             | 9.71| 2.65               | 17.54| 9.01| 0.999   | 0.902 |
| 6726 Hz   | -0.96            | 9.48| 8.97               | 11.57| 11.36| 2.55   | 11.11 |
| 7996 Hz   | -15.24           | 12.78| 12.90              | 13.14| 2.07| 12.48   | 1.00  |
Table 8. DPOAE levels in male non-smokers and female non-smokers.

| Frequency (Hz) | Male non-smokers | Female non-smokers |
|---------------|------------------|--------------------|
|               | Mean  | SD   | Mean  | SD   | Mean  | SD   | Mean  | SD   | Mean  | SD   |
| 842           | 5.47  | 6.35 | –3.71 | 6.18 | 6.29  | 2.71 | 5.71  | 4.90 | 7.61  | 4.82 |
| 1001          | 6.37  | 9.49 | –5.24 | 3.81 | 11.61 | 4.75 | 6.14  | –5.64 | 2.84  | 12.29 |
| 1184          | 7.16  | 6.40 | –7.08 | 3.99 | 14.24 | 6.46 | 6.75  | 5.88  | –6.98 | 2.92  | 13.71 | 5.48  |
| 1416          | 9.23  | 7.53 | –7.11 | 3.45 | 16.05 | 8.35 | 8.19  | –8.78 | 3.45  | 16.08 | 7.54  |
| 1685          | 11.42 | 5.02 | –8.00 | 3.06 | 19.42 | 5.91 | 8.30 | –7.47 | 2.58  | 15.77 | 7.01  |
| 2002          | 9.06  | 8.03 | –8.80 | 2.09 | 17.86 | 8.80 | 6.95  | –9.72 | 2.30  | 16.67 | 6.44  |
| 2380          | 7.09  | 7.27 | –9.97 | 2.50 | 17.06 | 7.49 | 7.23 | 5.57  | –9.98 | 2.55  | 17.22 | 5.34  |
| 2832          | 6.88  | 9.86 | –10.75 | 1.68 | 17.64 | 10.17 | 7.80 | 4.30 | –9.92 | 1.91  | 17.72 | 4.40  |
| 3369          | 7.22  | 8.76 | –10.83 | 1.80 | 17.22 | 8.95 | 7.81 | 5.67 | –10.14 | 1.89 | 18.09 | 6.01 |
| 4004          | 9.74  | 7.93 | –9.78 | 1.77 | 19.32 | 8.19 | 10.64 | 5.33 | –9.93 | 1.77 | 20.57 | 5.55  |
| 4761          | 10.91 | 6.83 | –9.27 | 2.14 | 20.18 | 6.58 | 11.69 | 7.30 | –9.53 | 2.27 | 21.23 | 6.94  |
| 5652          | 6.76  | 9.10 | –10.14 | 2.68 | 16.90 | 8.43 | 7.59 | 8.45 | –10.11 | 2.86 | 17.48 | 7.95  |
| 6726          | 6.76 | –0.90 | 12.07 | –11.48 | 2.95 | 10.58 | 10.74 | 1.92 | 9.35 | –11.33 | 2.36 | 13.24 | 9.31 |
| 7996          | –11.06 | 12.84 | –14.39 | 2.57 | 3.33 | 11.75 | –12.79 | 13.35 | –13.65 | 2.42 | 0.22 | 11.38 |

Table 9. DPOAE levels in male smokers and male non-smokers.

| Frequency (Hz) | Male smokers | Male non-smokers |
|---------------|--------------|------------------|
|               | Mean  | SD   | Noise | Mean  | SD   | Noise | SNR | Mean  | SD   | Noise | SNR | Mean  | SD   | Noise | SNR |
| 842           | 2.93  | 6.21 | –3.62 | 4.21 | 6.51 | 6.47 | 5.47 | 6.35 | –3.71 | 4.14 | 9.18 | 6.29 |
| 1001          | 2.89  | 6.02 | –5.76 | 3.02 | 8.65 | 5.40 | 6.37 | 9.49 | –5.24 | 3.81 | 11.61 | 9.71 |
| 1184          | 5.51  | 7.71 | –6.12 | 3.10 | 11.63 | 7.13 | 7.16 | 6.40 | –7.08 | 3.99 | 14.24 | 6.46 |
| 1416          | 5.82  | 9.81 | –6.86 | 3.68 | 12.69 | 8.14 | 9.23 | 7.53 | –7.11 | 3.45 | 16.05 | 8.35 |
| 1685          | 6.73  | 6.57 | –8.30 | 2.74 | 15.10 | 5.93 | 11.42 | 5.02 | –8.00 | 3.06 | 19.42 | 5.91 |
| 2002          | 6.14  | 5.56 | –9.06 | 2.49 | 15.20 | 5.46 | 9.06 | 8.03 | –8.80 | 2.09 | 17.86 | 8.80 |
| 2380          | 4.68  | 7.01 | –9.63 | 1.96 | 14.31 | 6.82 | 7.78 | 7.27 | –9.76 | 2.50 | 17.00 | 7.49 |
| 2832          | 4.05  | 9.39 | –10.22 | 2.58 | 14.28 | 8.48 | 8.88 | 9.86 | –10.75 | 1.68 | 17.64 | 10.17 |
| 3369          | 6.53  | 6.82 | –9.48 | 3.78 | 16.50 | 6.90 | 7.22 | 8.76 | –10.00 | 1.82 | 17.22 | 8.95 |
| 4004          | 7.84  | 9.45 | –9.56 | 1.73 | 17.63 | 9.13 | 9.74 | 7.93 | –9.78 | 1.77 | 19.32 | 8.19 |
| 4761          | 8.55  | 9.49 | –9.72 | 2.31 | 18.27 | 9.01 | 10.91 | 6.83 | –9.27 | 2.14 | 20.18 | 6.58 |
| 5652          | 5.98  | 9.67 | –8.77 | 2.01 | 14.75 | 9.21 | 6.76 | 9.10 | –10.14 | 2.68 | 16.90 | 8.43 |
| 6726          | 0.96  | 9.67 | –9.98 | 3.89 | 9.48 | 8.97 | –9.09 | 12.07 | –11.48 | 2.95 | 10.58 | 10.74 |
| 7996          | –15.24 | 13.81 | –13.12 | 2.23 | –2.11 | 12.78 | –11.06 | 12.84 | –14.39 | 2.57 | 3.33 | 11.75 |

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male smokers and non-smokers, respectively, and in 47.6% and 60.5% of female smokers and non-smokers, respectively. This clearly shows that men are more susceptible to smoking-induced hearing impairment.

**Discussion**

The effects of isolated exposure to tobacco smoke are extremely difficult to determine because smokers are frequently co-exposed to other ototoxic factors, especially in an occupational setting [18–20]. Moreover, the differences in male and female physiology should be considered; namely, the potential protective effect of hormonal factors on the female hearing organ [21,22]. Finally, the accurate evaluation of the hearing effects requires a group of individuals with sufficiently long and extensive exposure to the components of tobacco smoke. Furthermore, the selection of an appropriate method for hearing examination is an important issue since not every test is suitable for detection of changes at a subclinical level. Evaluation of otoacoustic emissions is an objective and highly sensitive method for hearing assessment [16–18,23,24]. The sensitivity of this test can be improved by the use of various intensities of L_1 and L_2 stimuli, as well as by the implementation of an input/output function [24–26].

The smokers and non-smokers participating in our study did not differ significantly in terms of their results of PTA at a 250–20 000 Hz frequency range. However, despite the lack of statistically significant differences, the hearing threshold of smokers was slightly higher than in non-smokers. This observation is consistent with the data published recently by Negley et al. [26]. Although the hearing threshold at a standard spectrum did not exceed 25 dB HL in any of the subjects participating in this study, the smokers presented with a 2–10 dB higher hearing thresholds than the controls. However, the smokers and non-smokers did not differ significantly in terms of their hearing thresholds at high frequencies [26]. In contrast, Paschoal and Azevedo [27] found significant differences in the audiometric hearing thresholds of smokers and non-smokers at 8 kHz, 12.5 kHz, and 14 kHz. Also, Oliveira and Lima [28] showed that the individuals who smoked for at least 5 years presented with significantly higher (albeit within a normal limit) hearing thresholds at a standard spectrum and at high frequencies than the subjects who never smoked. However, this study involved a relatively small sample of smokers (n=30), and its authors did not provide information about the daily number of cigarettes smoked in this group [28]. Basar and Belgin [29] examined 30 individuals with a 10-year history of smoking at least 1 package per day and 20 non-smoking controls, and found that the former presented with significantly higher hearing thresholds solely at 16 kHz and 18 kHz. Sousa et al. [30]

### Table 10. DPOAE levels in female smokers and female non-smokers.

| Frequency (Hz) | Female smokers | | | | Female non-smokers | | | |
|---------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|               | Mean | SD | Mean | SD | Noise | SNR | Mean | SD | Noise | SNR | P | DP | noise | SNR |
| 842 Hz        | 5.50 | 5.37 | –4.00 | 3.44 | 9.50 | 4.99 | 2.71 | 5.71 | –4.90 | 3.61 | 7.61 | 4.82 | 0.311 | 0.980 | 0.717 |
| 1001 Hz       | 5.59 | 7.64 | –5.93 | 4.07 | 11.52 | 6.06 | 4.75 | 6.14 | –6.54 | 2.84 | 11.29 | 6.09 | 1.000 | 0.999 | 1.000 |
| 1184 Hz       | 8.07 | 7.50 | –6.09 | 4.10 | 14.16 | 6.64 | 6.75 | 5.88 | –6.98 | 2.92 | 13.71 | 5.48 | 0.997 | 0.976 | 0.901 |
| 1416 Hz       | 9.75 | 6.97 | –6.30 | 3.94 | 16.05 | 6.98 | 8.19 | 8.48 | –7.88 | 3.45 | 16.08 | 7.54 | 0.996 | 0.482 | 1.000 |
| 1685 Hz       | 9.86 | 6.96 | –7.94 | 2.79 | 17.80 | 6.77 | 8.30 | 6.34 | –7.47 | 2.58 | 15.77 | 7.01 | 0.982 | 0.999 | 0.901 |
| 2002 Hz       | 8.40 | 6.58 | –9.19 | 2.74 | 17.59 | 5.90 | 6.95 | 6.64 | –9.72 | 2.30 | 16.67 | 6.44 | 0.989 | 0.993 | 1.000 |
| 2380 Hz       | 7.55 | 7.07 | –9.42 | 2.62 | 16.97 | 7.11 | 7.23 | 5.57 | –9.98 | 2.55 | 17.22 | 5.34 | 1.000 | 0.991 | 1.000 |
| 2832 Hz       | 5.64 | 8.54 | –10.41 | 2.10 | 16.07 | 7.78 | 7.80 | 4.30 | –9.92 | 1.91 | 17.72 | 4.40 | 0.863 | 0.976 | 0.965 |
| 3369 Hz       | 8.10 | 6.74 | –10.09 | 2.50 | 18.19 | 5.92 | 7.91 | 5.67 | –10.14 | 1.89 | 18.05 | 6.01 | 1.000 | 1.000 | 1.000 |
| 4004 Hz       | 10.41 | 6.71 | –9.98 | 2.27 | 20.39 | 6.25 | 10.64 | 5.33 | –9.93 | 1.77 | 20.57 | 5.55 | 1.000 | 1.000 | 1.000 |
| 4761 Hz       | 11.75 | 7.36 | –9.28 | 1.91 | 21.34 | 6.30 | 11.69 | 7.30 | –9.53 | 2.27 | 21.23 | 6.94 | 1.000 | 1.000 | 1.000 |
| 5652 Hz       | 7.80 | 10.29 | –9.74 | 2.65 | 17.54 | 9.01 | 7.59 | 8.45 | –10.11 | 2.86 | 17.48 | 7.95 | 1.000 | 1.000 | 1.000 |
| 6726 Hz       | –0.26 | 11.57 | –11.36 | 2.55 | 11.11 | 10.44 | 1.92 | 9.35 | –11.33 | 2.36 | 13.24 | 9.31 | 0.996 | 1.000 | 0.994 |
| 7996 Hz       | –15.46 | 12.90 | –13.14 | 2.07 | –1.26 | 12.48 | –12.79 | 13.35 | –13.65 | 2.42 | 11.38 | 0.997 | 0.991 | 1.000 |
Table 11. DPOAE levels – I/O analysis in smokers and non-smokers.

| L2 level dB SPL | Smokers | Non smokers | p | Smokers | Non-smokers | p |
|-----------------|---------|-------------|---|---------|-------------|---|
|                 | n       | mean        | SD | n       | mean        | SD | n       | mean        | SD | n       | mean        | SD | n       | mean        | SD |
| 1000 Hz DPOAE levels |         |             |    |         |             |    |         |             |    |         |             |    |         |             |    |
| 70              | 82      | 9.38        | 5.95 | 80      | 9.67        | 6.69 | 0.766 | 82      | 12.19      | 5.56 | 80      | 13.06      | 6.64 | 0.368 |
| 65              | 84      | 6.88        | 6.96 | 81      | 7.31        | 5.86 | 0.666 | 84      | 9.61       | 6.01 | 81      | 10.86      | 6.23 | 0.192 |
| 60              | 84      | 6.14        | 7.34 | 78      | 7.16        | 5.33 | 0.319 | 84      | 8.81       | 6.82 | 78      | 11.03      | 5.77 | 0.027 |
| 55              | 82      | 5.08        | 6.32 | 77      | 5.43        | 7.12 | 0.745 | 82      | 9.15       | 5.75 | 77      | 9.82       | 6.31 | 0.482 |
| 50              | 79      | 3.27        | 6.61 | 75      | 3.76        | 7.58 | 0.675 | 79      | 8.00       | 6.25 | 75      | 9.18       | 7.16 | 0.276 |
| 45              | 75      | 0.96        | 7.04 | 72      | 2.79        | 6.11 | 0.095 | 75      | 6.09       | 6.40 | 72      | 8.44       | 5.83 | 0.022 |
| 40              | 64      | –2.44       | 9.69 | 68      | –0.73       | 8.43 | 0.282 | 64      | 3.34       | 8.17 | 68      | 5.55       | 7.54 | 0.108 |
| 1500 Hz DPOAE levels |         |             |    |         |             |    |         |             |    |         |             |    |         |             |    |
| 70              | 85      | 11.92       | 7.65 | 81      | 13.49       | 5.45 | 0.131 | 85      | 16.80      | 7.85 | 81      | 20.38      | 6.41 | 0.002 |
| 65              | 84      | 10.70       | 8.33 | 80      | 12.41       | 5.30 | 0.122 | 84      | 15.39      | 8.00 | 80      | 18.17      | 5.95 | 0.013 |
| 60              | 85      | 9.56        | 7.09 | 79      | 10.97       | 5.88 | 0.169 | 85      | 14.76      | 6.19 | 79      | 16.75      | 5.99 | 0.039 |
| 55              | 84      | 7.55        | 8.04 | 80      | 8.93        | 8.26 | 0.441 | 84      | 13.26      | 7.18 | 80      | 14.63      | 7.76 | 0.247 |
| 50              | 83      | 5.22        | 8.62 | 80      | 6.47        | 7.52 | 0.324 | 83      | 11.40      | 7.05 | 80      | 12.92      | 6.86 | 0.167 |
| 45              | 79      | 3.38        | 7.79 | 79      | 4.95        | 7.28 | 0.192 | 79      | 10.34      | 5.99 | 79      | 12.07      | 6.84 | 0.094 |
| 40              | 76      | 0.02        | 9.73 | 78      | 1.82        | 8.62 | 0.223 | 76      | 7.04       | 7.82 | 78      | 9.83       | 7.81 | 0.028 |
| 2000 Hz DPOAE levels |         |             |    |         |             |    |         |             |    |         |             |    |         |             |    |
| 70              | 86      | 11.90       | 5.31 | 81      | 12.07       | 5.78 | 0.841 | 86      | 19.75      | 6.33 | 81      | 21.27      | 6.28 | 0.122 |
| 65              | 86      | 10.89       | 5.51 | 81      | 11.24       | 5.81 | 0.690 | 86      | 18.00      | 6.06 | 81      | 19.65      | 6.13 | 0.082 |
| 60              | 86      | 8.67        | 7.43 | 80      | 10.16       | 6.17 | 0.163 | 86      | 16.23      | 7.35 | 80      | 18.60      | 6.81 | 0.033 |
| 55              | 84      | 7.62        | 5.92 | 81      | 8.23        | 6.35 | 0.523 | 84      | 15.34      | 6.07 | 81      | 17.41      | 6.45 | 0.035 |
| 50              | 84      | 4.93        | 7.56 | 79      | 6.03        | 7.65 | 0.358 | 84      | 13.55      | 7.18 | 79      | 15.03      | 7.57 | 0.202 |
| 45              | 83      | 2.90        | 6.44 | 80      | 2.88        | 8.68 | 0.984 | 83      | 11.77      | 6.17 | 80      | 12.63      | 7.76 | 0.431 |
| 40              | 76      | 0.05        | 7.73 | 79      | –1.13       | 10.40 | 0.426 | 76      | 8.88       | 6.36 | 79      | 8.86       | 9.63 | 0.991 |
| 3000 Hz DPOAE levels |         |             |    |         |             |    |         |             |    |         |             |    |         |             |    |
| 70              | 85      | 10.19       | 5.57 | 81      | 11.08       | 5.67 | 0.310 | 85      | 20.45      | 5.85 | 81      | 22.11      | 6.07 | 0.073 |
| 65              | 85      | 9.18        | 6.23 | 81      | 9.93        | 6.50 | 0.446 | 85      | 18.54      | 6.13 | 81      | 19.81      | 6.93 | 0.210 |
| 60              | 86      | 7.42        | 6.41 | 81      | 8.69        | 5.84 | 0.184 | 86      | 16.59      | 6.54 | 81      | 18.60      | 5.83 | 0.038 |
| 55              | 86      | 5.98        | 7.22 | 82      | 7.20        | 7.27 | 0.277 | 86      | 15.56      | 6.73 | 82      | 17.20      | 7.30 | 0.130 |
| 50              | 86      | 3.94        | 8.12 | 82      | 5.65        | 6.34 | 0.131 | 86      | 13.89      | 6.77 | 82      | 15.84      | 5.93 | 0.049 |
| 45              | 83      | 0.29        | 11.46 | 82      | 2.79        | 7.70 | 0.102 | 83      | 10.43      | 9.64 | 82      | 13.76      | 7.59 | 0.015 |
| 40              | 79      | –0.98       | 10.26 | 80      | 0.65        | 7.27 | 0.248 | 79      | 10.07      | 8.55 | 80      | 11.66      | 6.73 | 0.196 |
analyzed the exposure of 625 volunteers to various risk factors of hearing impairment. Neither PTA nor speech audiometry confirmed the role of tobacco smoking as a risk factor for this condition [30]. The influence of tobacco smoking and noise on hearing, examined by means of tone audiometry at a standard spectrum, was also analyzed by Pouryaghoub et al. [20]; they found that a group of 206 smokers was characterized by significantly higher hearing threshold at 4 kHz when compared to 206 non-smoking controls.

Aside from smoking, the hearing impairment documented in some of our participants might be related to their sex, age (up to 67 years), and/or exposure to noise [20]. An important study analyzing the effect of sex on the auditory consequences of smoking was conducted by Uchida et al. [31]. They found that the results of PTA at 4000 Hz were significantly worse in male smokers than in male non-smokers, but a similar phenomenon was not observed in the case of female smokers and non-smokers [31]. Nomura et al. [32] conducted a meta-analysis of 15 studies published between 1966 and 2003, in order to determine the effects of cigarette smoking on the results of

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Table 11 continued. DPOAE levels – I/O analysis in smokers and non-smokers.

| L2 level dB SPL | Smokers | | | Non-smokers | | | | | p | Smokers | | | Non-smokers | | | | | 4000 Hz DPOAE levels | 4000 Hz SNR analysis |
|----------------|---------|---|---|----------------|---|---|---|---|---|---------|---|---|---|---|---|---|---|---|
| 70             | 86      | 13.74 | 6.29 | 80             | 14.38 | 5.18 | 0.475 | 86             | 23.71 | 6.70 | 80             | 25.52 | 5.45 | 0.060 |
| 65             | 86      | 12.66 | 6.58 | 80             | 13.40 | 5.07 | 0.422 | 86             | 21.85 | 6.68 | 80             | 23.60 | 5.04 | 0.061 |
| 60             | 85      | 11.25 | 6.83 | 81             | 11.62 | 6.00 | 0.709 | 85             | 20.86 | 6.73 | 81             | 21.54 | 6.29 | 0.502 |
| 55             | 84      | 9.91  | 7.63 | 81             | 10.25 | 6.25 | 0.757 | 84             | 19.36 | 7.17 | 81             | 20.09 | 6.02 | 0.476 |
| 50             | 86      | 7.21  | 9.42 | 81             | 8.41  | 5.95 | 0.331 | 86             | 17.24 | 8.60 | 81             | 18.61 | 5.76 | 0.232 |
| 45             | 85      | 4.47  | 10.40| 81             | 5.79  | 7.47 | 0.322 | 85             | 14.42 | 9.01 | 81             | 16.15 | 6.94 | 0.170 |
| 40             | 84      | 1.75  | 10.99| 80             | 3.59  | 6.80 | 0.203 | 84             | 11.57 | 9.47 | 80             | 13.73 | 6.58 | 0.094 |

| 5000 Hz DPOAE levels | 5000 Hz SNR analysis |
|-----------------------|-----------------------|
| 70                     | 85                   |
| 14.12                  | 8.10                 |
| 82                     | 12.09                |
| 8.38                   | 0.816                |
| 85                     | 21.32                |
| 7.18                   | 82                   |
| 21.81                  | 7.50                 |
| 0.671                  |                      |
| 65                     | 86                   |
| 12.37                  | 7.57                 |
| 82                     | 12.09                |
| 8.38                   | 0.816                |
| 85                     | 21.32                |
| 7.18                   | 82                   |
| 21.81                  | 7.50                 |
| 0.671                  |                      |
| 60                     | 86                   |
| 10.85                  | 7.95                 |
| 82                     | 10.84                |
| 8.72                   | 0.991                |
| 86                     | 19.92                |
| 7.53                   | 82                   |
| 20.60                  | 8.09                 |
| 0.572                  |                      |
| 55                     | 85                   |
| 8.78                   | 7.99                 |
| 81                     | 9.46                 |
| 7.15                   | 0.566                |
| 85                     | 18.07                |
| 6.98                   | 81                   |
| 19.15                  | 5.91                 |
| 0.287                  |                      |
| 50                     | 84                   |
| 5.99                   | 9.37                 |
| 82                     | 6.47                 |
| 8.89                   | 0.735                |
| 84                     | 15.80                |
| 7.61                   | 82                   |
| 16.54                  | 7.91                 |
| 0.539                  |                      |
| 45                     | 85                   |
| 3.22                   | 10.48               |
| 82                     | 4.40                 |
| 9.59                   | 0.450                |
| 85                     | 13.46                |
| 8.52                   | 82                   |
| 14.71                  | 8.55                 |
| 0.343                  |                      |
| 40                     | 83                   |
| –0.18                  | 11.95               |
| 80                     | 2.45                 |
| 7.68                   | 0.098                |
| 83                     | 9.96                 |
| 9.92                   | 80                   |
| 12.58                  | 6.81                 |
| 0.052                  |                      |

| 6000 Hz DPOAE levels | 6000 Hz SNR analysis |
|----------------------|----------------------|
| 70                    | 86                   |
| 13.56                 | 9.39                 |
| 82                    | 14.05                |
| 7.72                  | 0.717                |
| 86                    | 23.99                |
| 9.39                 | 82                   |
| 25.08                  | 7.79                 |
| 0.418                 |                      |
| 65                    | 84                   |
| 12.22                 | 8.22                 |
| 80                    | 12.53                |
| 7.62                  | 0.801                |
| 84                    | 21.77                |
| 7.71                 | 80                   |
| 22.51                  | 7.38                 |
| 0.534                 |                      |
| 60                    | 86                   |
| 9.02                  | 10.01               |
| 80                    | 10.09                |
| 7.46                  | 0.441                |
| 86                    | 18.92                |
| 8.74                 | 80                   |
| 19.98                  | 7.01                 |
| 0.389                 |                      |
| 55                    | 83                   |
| 6.63                  | 11.00               |
| 81                    | 6.85                 |
| 8.48                  | 0.885                |
| 83                    | 16.78                |
| 9.51                 | 81                   |
| 16.94                  | 8.00                 |
| 0.905                 |                      |
| 50                    | 84                   |
| 2.36                  | 13.19               |
| 81                    | 4.01                 |
| 8.68                  | 0.346                |
| 84                    | 12.78                |
| 11.43                | 81                   |
| 14.85                  | 7.46                 |
| 0.173                 |                      |
| 45                    | 81                   |
| –0.32                 | 12.88               |
| 80                    | 0.25                 |
| 9.64                  | 0.751                |
| 81                    | 10.01                |
| 10.71                | 80                   |
| 11.48                  | 8.55                 |
| 0.340                 |                      |
| 40                    | 78                   |
| –4.29                 | 13.35               |
| 73                    | –4.02                |
| 11.54                 | 0.893                |
| 78                    | 6.65                 |
| 10.90                | 73                   |
| 7.72                  | 9.80                 |
| 0.528                 |                      |
Table 12. DPOAE levels – I/O analysis in male smokers and female smokers.

| L2 level dB SPL | Male smokers | Female smokers | 1000 Hz DPOAE levels | 1000 Hz SNR analysis | 1500 Hz DPOAE levels | 1500 Hz SNR analysis | 2000 Hz DPOAE levels | 2000 Hz SNR analysis | 3000 Hz DPOAE levels | 3000 Hz SNR analysis |
|-----------------|--------------|----------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
|                 | n | mean | SD | n | mean | SD | p | n | mean | SD | p | n | mean | SD | p | n | mean | SD | p | n | mean | SD | p |
| 70              | 40 | 9.74 | 5.51 | 42 | 9.03 | 6.38 | 0.590 | 40 | 12.25 | 5.66 | 42 | 12.13 | 5.53 | 0.924 |
| 65              | 43 | 5.76 | 7.02 | 41 | 8.06 | 6.77 | 0.131 | 43 | 8.38 | 6.74 | 41 | 10.90 | 4.90 | 0.053 |
| 60              | 43 | 4.67 | 7.71 | 41 | 7.69 | 6.69 | 0.058 | 43 | 7.17 | 7.39 | 41 | 10.54 | 5.75 | 0.022 |
| 55              | 41 | 3.60 | 6.08 | 41 | 6.56 | 6.29 | 0.034 | 41 | 7.77 | 6.16 | 41 | 10.52 | 5.03 | 0.030 |
| 50              | 40 | 1.93 | 6.26 | 39 | 4.66 | 6.75 | 0.067 | 40 | 6.04 | 6.81 | 39 | 10.01 | 4.94 | 0.004 |
| 45              | 36 | -0.69 | 6.73 | 39 | 2.48 | 7.07 | 0.050 | 36 | 4.43 | 7.16 | 39 | 7.62 | 5.25 | 0.033 |
| 40              | 30 | -3.44 | 9.07 | 34 | -1.55 | 10.26 | 0.436 | 30 | 2.15 | 7.46 | 34 | 4.39 | 8.71 | 0.273 |
| 70              | 44 | 10.49 | 7.26 | 41 | 13.45 | 7.84 | 0.075 | 44 | 15.90 | 7.55 | 41 | 17.77 | 8.15 | 0.276 |
| 65              | 43 | 8.81 | 8.90 | 41 | 12.68 | 7.28 | 0.032 | 43 | 13.91 | 8.32 | 41 | 16.93 | 7.42 | 0.083 |
| 60              | 43 | 8.08 | 6.13 | 42 | 11.07 | 7.73 | 0.052 | 43 | 14.12 | 5.59 | 42 | 15.42 | 6.75 | 0.339 |
| 55              | 42 | 6.01 | 6.61 | 42 | 9.09 | 9.08 | 0.080 | 42 | 12.15 | 6.21 | 42 | 14.37 | 7.95 | 0.157 |
| 50              | 42 | 2.74 | 9.62 | 41 | 7.75 | 6.67 | 0.007 | 42 | 9.92 | 7.78 | 41 | 12.92 | 5.93 | 0.051 |
| 45              | 39 | 2.18 | 6.28 | 40 | 4.54 | 8.95 | 0.178 | 39 | 10.14 | 5.29 | 40 | 10.55 | 6.65 | 0.764 |
| 40              | 42 | -1.66 | 8.57 | 34 | 2.10 | 10.57 | 0.099 | 42 | 6.31 | 7.80 | 34 | 7.29 | 7.86 | 0.370 |
| 70              | 44 | 10.66 | 4.62 | 42 | 13.20 | 5.72 | 0.026 | 44 | 18.10 | 5.84 | 42 | 21.49 | 6.43 | 0.012 |
| 65              | 44 | 9.51 | 4.98 | 42 | 12.33 | 5.72 | 0.017 | 44 | 16.67 | 6.09 | 42 | 19.40 | 5.76 | 0.035 |
| 60              | 44 | 6.83 | 8.19 | 42 | 10.60 | 6.06 | 0.017 | 44 | 14.44 | 8.20 | 42 | 18.10 | 5.87 | 0.020 |
| 55              | 42 | 6.57 | 5.41 | 42 | 8.66 | 6.27 | 0.106 | 42 | 14.45 | 5.96 | 42 | 16.23 | 6.12 | 0.182 |
| 50              | 43 | 3.24 | 8.31 | 41 | 6.70 | 6.31 | 0.034 | 43 | 12.20 | 7.94 | 41 | 14.96 | 6.06 | 0.076 |
| 45              | 42 | 1.58 | 5.96 | 41 | 4.27 | 6.70 | 0.057 | 42 | 10.74 | 6.96 | 41 | 12.81 | 5.11 | 0.126 |
| 40              | 38 | -2.09 | 8.18 | 38 | 2.19 | 6.70 | 0.015 | 38 | 7.10 | 6.77 | 38 | 10.65 | 5.43 | 0.014 |
| 70              | 43 | 9.85 | 5.04 | 42 | 10.54 | 6.1 | 0.571 | 43 | 20.00 | 5.28 | 50 | 22.41 | 4.57 | 0.481 |
| 65              | 43 | 8.54 | 6.36 | 42 | 9.83 | 6.11 | 0.342 | 43 | 17.62 | 6.58 | 50 | 20.05 | 4.29 | 0.165 |
| 60              | 44 | 6.68 | 6.55 | 42 | 8.20 | 6.24 | 0.274 | 44 | 15.82 | 5.91 | 50 | 18.63 | 5.19 | 0.261 |
| 55              | 44 | 4.91 | 7.98 | 42 | 7.11 | 6.23 | 0.157 | 44 | 14.46 | 7.23 | 50 | 17.67 | 4.78 | 0.121 |
| 50              | 44 | 2.78 | 8.99 | 42 | 5.15 | 7.00 | 0.175 | 44 | 12.78 | 7.71 | 50 | 15.86 | 4.51 | 0.119 |
| 45              | 43 | -0.87 | 12.06 | 40 | 1.53 | 10.80 | 0.343 | 43 | 9.27 | 10.39 | 50 | 13.73 | 7.21 | 0.258 |
| 40              | 40 | -3.29 | 12.61 | 39 | 1.38 | 6.45 | 0.042 | 40 | 8.29 | 10.72 | 50 | 10.95 | 7.13 | 0.060 |
PTA. They documented the unfavorable effect of smoking in 9 out of the 15 analyzed studies; the lack of such an association in the remaining studies suggests that the relationship between smoking and hearing impairment is still not completely understood [32].

Previous research on click-evoked otoacoustic emissions [27,33,34] showed that smokers present with lower CEOAE levels than non-smokers. Paschoal and Azevedo [27] did not observe CEOAEs in 13.9% and 2.8% of smokers and non-smokers, respectively (p=0.016). The levels of CEOAEs do not seem to be modulated by the age of smokers [34]. Interestingly, a study of CEOAEs in newborns whose mothers smoked during pregnancy demonstrated not only the functional impairment of sound perception, but also the structural abnormalities of the hearing organ [33]. In our study, male smokers presented with significantly lower CEOAE levels than male non-smokers and female smokers. To the best of our knowledge, this was the first study to demonstrate sex-specific differences in smokers’ CEOAE levels.

| L2 level dB SPL | Male smokers | Female smokers | p | Male smokers | Female smokers | p |
|----------------|--------------|----------------|---|--------------|----------------|---|
|                | n  | mean | SD | n  | mean | SD | n  | mean | SD | n  | mean | SD | n  | mean | SD | p |
| 4000 Hz DPOAE levels |    |       |   |    |       |   |    |       |   |    |       |   |    |       |   |   |
| 70             | 44 | 13.07 | 6.77 | 42 | 14.44 | 5.75 | 0.311 | 44 | 22.68 | 6.93 | 42 | 24.79 | 6.36 | 0.144 |
| 65             | 44 | 11.84 | 7.18 | 42 | 13.52 | 5.85 | 0.239 | 44 | 21.05 | 7.24 | 42 | 22.70 | 6.01 | 0.253 |
| 60             | 43 | 10.61 | 7.37 | 42 | 11.90 | 6.24 | 0.385 | 43 | 19.72 | 7.49 | 42 | 22.03 | 5.72 | 0.114 |
| 55             | 42 | 9.20  | 8.56 | 42 | 10.61 | 6.60 | 0.401 | 42 | 18.21 | 7.96 | 42 | 20.50 | 6.15 | 0.145 |
| 50             | 44 | 6.09  | 9.99 | 42 | 8.40  | 8.75 | 0.257 | 44 | 16.17 | 9.46 | 42 | 18.37 | 7.55 | 0.234 |
| 45             | 43 | 3.41  | 11.15| 42 | 5.55  | 9.59 | 0.346 | 43 | 13.21 | 10.03| 42 | 15.65 | 7.75 | 0.213 |
| 40             | 42 | 0.84  | 11.43| 42 | 2.67  | 10.59| 0.450 | 42 | 10.51 | 10.06| 42 | 12.62 | 8.85 | 0.309 |
| 5000 Hz DPOAE levels |    |       |   |    |       |   |    |       |   |    |       |   |    |       |   |   |
| 70             | 43 | 12.76 | 8.53 | 42 | 15.52 | 7.48 | 0.116 | 43 | 21.97 | 7.79 | 42 | 25.57 | 6.95 | 0.027 |
| 65             | 43 | 11.14 | 7.53 | 42 | 13.63 | 7.49 | 0.130 | 43 | 20.09 | 7.50 | 42 | 22.58 | 6.69 | 0.110 |
| 60             | 44 | 9.43  | 8.43 | 42 | 12.35 | 7.21 | 0.087 | 44 | 18.12 | 8.00 | 42 | 21.80 | 6.58 | 0.022 |
| 55             | 43 | 7.67  | 8.23 | 42 | 9.92  | 7.66 | 0.195 | 43 | 16.52 | 7.40 | 42 | 19.66 | 6.22 | 0.037 |
| 50             | 44 | 6.00  | 9.43 | 41 | 7.44  | 9.21 | 0.166 | 44 | 14.65 | 7.89 | 41 | 17.00 | 7.20 | 0.158 |
| 45             | 43 | 2.43  | 10.38| 42 | 4.03  | 10.65| 0.487 | 43 | 12.44 | 8.57 | 42 | 14.50 | 8.44 | 0.270 |
| 40             | 42 | -1.00 | 11.57| 41 | 0.66  | 12.41| 0.531 | 42 | 9.18  | 9.45 | 41 | 10.76 | 10.43| 0.470 |
| 6000 Hz DPOAE levels |    |       |   |    |       |   |    |       |   |    |       |   |    |       |   |   |
| 70             | 44 | 12.35 | 10.25| 42 | 14.84 | 8.32 | 0.219 | 44 | 22.65 | 10.64| 42 | 25.40 | 7.74 | 0.174 |
| 65             | 42 | 11.75 | 8.10 | 42 | 12.69 | 8.41 | 0.600 | 42 | 21.18 | 7.72 | 42 | 22.36 | 7.74 | 0.483 |
| 60             | 44 | 7.71  | 10.69| 42 | 10.40 | 9.16 | 0.214 | 44 | 17.61 | 9.69 | 42 | 20.28 | 7.49 | 0.156 |
| 55             | 43 | 5.73  | 10.40| 40 | 7.59  | 11.66| 0.446 | 43 | 15.62 | 9.31 | 40 | 18.03 | 9.68 | 0.252 |
| 50             | 43 | 1.76  | 12.21| 41 | 2.99  | 14.27| 0.671 | 43 | 12.29 | 10.90| 41 | 13.30 | 12.07| 0.690 |
| 45             | 42 | -2.10 | 13.28| 39 | 1.59  | 12.31| 0.197 | 42 | 8.59  | 11.32| 39 | 11.55 | 9.94 | 0.214 |
| 40             | 38 | -5.92 | 13.34| 40 | -2.75 | 13.34| 0.297 | 38 | 5.13  | 11.00| 40 | 8.09  | 10.74| 0.232 |
| L2 level dB SPL | Male non-smokers | | Female non-smokers | | | p | Male non-smokers | | Female non-smokers | | | p |
|-----------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| 1000 Hz DPOAE levels | | | | | | | | | | | | | |
| 70 | 31 | 9.83 | 8.57 | 49 | 9.57 | 5.27 | 0.880 | 31 | 12.63 | 7.85 | 49 | 13.33 | 5.81 | 0.320 |
| 65 | 32 | 8.21 | 5.87 | 49 | 6.73 | 5.83 | 0.269 | 32 | 11.06 | 7.22 | 49 | 10.73 | 5.57 | 0.880 |
| 60 | 29 | 8.33 | 4.62 | 49 | 6.46 | 5.63 | 0.115 | 29 | 11.76 | 5.33 | 49 | 10.60 | 6.02 | 0.957 |
| 55 | 31 | 5.87 | 8.67 | 46 | 5.13 | 5.94 | 0.677 | 31 | 9.38 | 8.29 | 46 | 10.12 | 4.60 | 0.695 |
| 50 | 30 | 5.32 | 6.36 | 45 | 2.72 | 8.19 | 0.127 | 30 | 10.01 | 5.25 | 45 | 8.63 | 8.20 | 0.362 |
| 45 | 30 | 3.34 | 7.00 | 42 | 2.40 | 5.44 | 0.543 | 30 | 8.47 | 6.32 | 42 | 8.41 | 5.54 | 0.513 |
| 40 | 26 | 1.72 | 6.14 | 42 | –2.25 | 9.33 | 0.038 | 26 | 6.82 | 6.45 | 42 | 4.77 | 8.11 | 0.844 |
| 1500 Hz DPOAE levels | | | | | | | | | | | | | |
| 70 | 32 | 13.85 | 5.59 | 49 | 13.26 | 5.40 | 0.637 | 32 | 20.27 | 7.03 | 49 | 20.45 | 6.05 | 0.903 |
| 65 | 32 | 12.62 | 5.65 | 48 | 12.27 | 5.10 | 0.779 | 32 | 18.24 | 6.16 | 48 | 18.13 | 5.88 | 0.936 |
| 60 | 32 | 10.89 | 6.76 | 47 | 11.03 | 5.28 | 0.923 | 32 | 16.56 | 6.29 | 47 | 16.87 | 5.84 | 0.824 |
| 55 | 31 | 7.33 | 7.33 | 49 | 8.01 | 8.82 | 0.460 | 31 | 15.29 | 7.75 | 49 | 14.21 | 7.82 | 0.549 |
| 50 | 31 | 7.14 | 8.11 | 49 | 6.05 | 7.18 | 0.541 | 31 | 13.34 | 7.22 | 49 | 12.65 | 6.69 | 0.670 |
| 45 | 30 | 6.17 | 6.96 | 49 | 4.20 | 7.44 | 0.238 | 30 | 12.81 | 6.40 | 49 | 11.62 | 7.12 | 0.446 |
| 40 | 29 | 1.99 | 10.67 | 49 | 1.72 | 7.26 | 0.905 | 29 | 9.46 | 9.80 | 49 | 10.05 | 6.46 | 0.775 |
| 2000 Hz DPOAE levels | | | | | | | | | | | | | |
| 70 | 31 | 13.19 | 6.17 | 50 | 11.38 | 5.47 | 0.185 | 31 | 22.45 | 6.30 | 50 | 20.54 | 6.22 | 0.188 |
| 65 | 31 | 12.13 | 6.36 | 50 | 10.68 | 5.44 | 0.296 | 31 | 20.03 | 6.69 | 50 | 19.42 | 5.81 | 0.676 |
| 60 | 30 | 11.11 | 7.14 | 50 | 9.59 | 5.50 | 0.320 | 30 | 19.36 | 7.74 | 50 | 18.15 | 6.22 | 0.471 |
| 55 | 31 | 9.12 | 7.52 | 50 | 7.68 | 5.50 | 0.361 | 31 | 18.53 | 7.56 | 50 | 16.72 | 5.63 | 0.255 |
| 50 | 30 | 6.76 | 10.01 | 49 | 5.58 | 5.82 | 0.560 | 30 | 15.22 | 10.43 | 49 | 14.91 | 5.22 | 0.881 |
| 45 | 31 | 4.22 | 8.15 | 49 | 2.03 | 8.98 | 0.264 | 31 | 13.34 | 7.77 | 49 | 12.19 | 7.80 | 0.522 |
| 40 | 31 | –0.37 | 10.73 | 48 | –1.61 | 10.26 | 0.611 | 31 | 9.02 | 10.26 | 48 | 8.76 | 9.32 | 0.911 |
| 3000 Hz DPOAE levels | | | | | | | | | | | | | |
| 70 | 31 | 11.26 | 7.17 | 50 | 10.97 | 4.58 | 0.844 | 31 | 21.63 | 7.99 | 50 | 22.41 | 4.57 | 0.624 |
| 65 | 31 | 9.72 | 8.91 | 50 | 10.07 | 4.50 | 0.841 | 31 | 19.43 | 9.88 | 50 | 20.05 | 4.29 | 0.739 |
| 60 | 31 | 8.86 | 6.90 | 50 | 8.58 | 5.15 | 0.846 | 31 | 18.54 | 5.83 | 50 | 18.63 | 5.19 | 0.949 |
| 55 | 32 | 6.89 | 9.75 | 50 | 7.41 | 5.22 | 0.783 | 32 | 16.47 | 10.11 | 50 | 17.67 | 4.78 | 0.534 |
| 50 | 32 | 5.70 | 7.58 | 50 | 5.61 | 5.48 | 0.953 | 32 | 15.81 | 7.73 | 50 | 15.86 | 4.51 | 0.974 |
| 45 | 32 | 3.32 | 7.56 | 50 | 2.46 | 7.84 | 0.623 | 32 | 13.82 | 8.26 | 50 | 13.73 | 7.21 | 0.960 |
| 40 | 30 | 2.34 | 5.53 | 50 | –0.37 | 8.02 | 0.078 | 30 | 12.83 | 5.94 | 50 | 10.95 | 7.13 | 0.208 |
Apart from CEOAEs, we evaluated otoacoustic emissions as a DP-gran function. Negley et al. [26] analyzed the DP-grams obtained using high \( L_2 \) level of stimulation, and showed that smokers presented with significantly lower DPOAE levels at all frequencies. In contrast, we used \( L_2 = 71 \text{ dB SPL} \) intensity of stimulation, and showed that smokers presented with significantly lower DPOAE levels than non-smokers on most comparisons, also when adjusted for sex. Torre et al. [35] did not find a significant effect of smoking on DPOAE levels (2.3–8.0 kHz), but their results might have been confounded by selection bias, since it included subjects who smoked no longer than for 1 year, which might be an insufficient exposure to tobacco smoke [35]. Furthermore, we showed that compared to male non-smokers, male long-term smokers presented with significantly lower DPOAE levels at 1685 Hz; this suggests a sex-specific effect of smoking on DPOAEs.

The results of our analysis of DPOAEs in an input/output function, being a highly sensitive test for the active and passive mechanisms of the cochlea, are consistent with the data published by Negley et al. [26]. These authors showed that a gradual increase

| L2 level dB SPL | Male non-smokers | Female non-smokers | p | Male non-smokers | Female non-smokers |
|----------------|------------------|--------------------|---|------------------|--------------------|
|                | n | mean | SD | n | mean | SD | n | mean | SD | n | mean | SD |
| 4000 Hz DPOAE levels | 70 | 30 | 14.84 | 5.11 | 50 | 14.11 | 5.26 | 0.544 | 30 | 25.95 | 5.40 | 50 | 25.26 | 5.52 | 0.585 |
|                | 65 | 30 | 13.70 | 5.12 | 50 | 13.22 | 5.08 | 0.664 | 30 | 23.71 | 4.50 | 50 | 23.53 | 5.37 | 0.875 |
|                | 60 | 31 | 11.23 | 7.24 | 50 | 11.87 | 5.15 | 0.672 | 31 | 20.81 | 7.77 | 50 | 22.00 | 5.21 | 0.453 |
|                | 55 | 31 | 9.94 | 7.31 | 50 | 10.43 | 5.56 | 0.749 | 31 | 18.97 | 7.30 | 50 | 20.79 | 5.02 | 0.229 |
|                | 50 | 31 | 8.09 | 6.64 | 50 | 8.61 | 5.54 | 0.716 | 31 | 17.69 | 6.83 | 50 | 19.18 | 4.98 | 0.298 |
|                | 45 | 31 | 5.62 | 7.40 | 50 | 5.89 | 7.59 | 0.875 | 31 | 15.45 | 7.62 | 50 | 16.58 | 6.54 | 0.500 |
|                | 40 | 32 | 2.76 | 7.67 | 48 | 4.14 | 6.17 | 0.397 | 32 | 12.48 | 7.47 | 48 | 14.55 | 5.84 | 0.191 |
| 5000 Hz DPOAE levels | 70 | 32 | 13.56 | 8.61 | 50 | 13.77 | 6.51 | 0.497 | 32 | 24.26 | 8.33 | 50 | 25.47 | 6.35 | 0.488 |
|                | 65 | 32 | 11.25 | 9.94 | 50 | 12.62 | 7.27 | 0.504 | 32 | 20.91 | 9.20 | 50 | 22.38 | 6.20 | 0.428 |
|                | 60 | 32 | 10.38 | 8.61 | 50 | 11.14 | 8.86 | 0.702 | 32 | 19.69 | 8.46 | 50 | 21.18 | 7.87 | 0.425 |
|                | 55 | 31 | 9.47 | 6.42 | 50 | 9.45 | 7.64 | 0.989 | 31 | 18.73 | 5.27 | 50 | 19.41 | 6.31 | 0.603 |
|                | 50 | 32 | 5.48 | 9.93 | 50 | 7.10 | 8.19 | 0.443 | 32 | 15.65 | 9.17 | 50 | 17.11 | 7.03 | 0.447 |
|                | 45 | 32 | 2.81 | 11.40 | 50 | 5.42 | 8.20 | 0.266 | 32 | 12.96 | 10.75 | 50 | 15.84 | 6.67 | 0.182 |
|                | 40 | 31 | 1.00 | 8.67 | 49 | 3.36 | 6.92 | 0.207 | 31 | 10.94 | 7.08 | 49 | 13.62 | 6.50 | 0.093 |
| 6000 Hz DPOAE levels | 70 | 32 | 14.22 | 8.87 | 50 | 13.93 | 6.97 | 0.878 | 32 | 24.90 | 8.76 | 50 | 25.19 | 7.20 | 0.875 |
|                | 65 | 30 | 13.36 | 8.64 | 50 | 12.04 | 6.98 | 0.480 | 30 | 22.99 | 8.57 | 50 | 22.22 | 6.65 | 0.675 |
|                | 60 | 30 | 11.31 | 6.75 | 50 | 9.35 | 7.83 | 0.241 | 30 | 20.69 | 6.87 | 50 | 19.56 | 7.13 | 0.485 |
|                | 55 | 32 | 6.76 | 10.18 | 49 | 6.91 | 7.27 | 0.944 | 32 | 15.87 | 10.15 | 49 | 17.64 | 6.23 | 0.381 |
|                | 50 | 32 | 4.40 | 8.46 | 49 | 3.75 | 8.90 | 0.743 | 32 | 14.60 | 8.04 | 49 | 15.01 | 7.14 | 0.816 |
|                | 45 | 32 | -0.07 | 9.98 | 48 | 0.46 | 9.51 | 0.813 | 32 | 10.48 | 9.44 | 48 | 12.14 | 7.94 | 0.418 |
|                | 40 | 31 | -4.95 | 12.25 | 42 | -3.34 | 11.09 | 0.566 | 31 | 6.37 | 10.34 | 42 | 8.71 | 9.39 | 0.323 |
## Table 14. DPOAE levels – I/O analysis in male smokers and male non-smokers.

| L2 level dB SPL | 1000 Hz DPOAE levels | 1000 Hz SNR analysis | 1500 Hz DPOAE levels | 1500 Hz SNR analysis | 2000 Hz DPOAE levels | 2000 Hz SNR analysis | 3000 Hz DPOAE levels | 3000 Hz SNR analysis |
|-----------------|------------------------|-----------------------|------------------------|-----------------------|------------------------|-----------------------|------------------------|-----------------------|
|                 | Male smokers           | Male non-smokers      | Male smokers           | Male non-smokers      | Male smokers           | Male non-smokers      | Male smokers           | Male non-smokers      |
|                 | n | mean | SD | n | mean | SD | p | n | mean | SD | n | mean | SD | p | n | mean | SD | p |
| 70              | 40 | 9.74 | 5.51 | 31 | 9.83 | 8.57 | 0.956 | 40 | 12.25 | 5.66 | 31 | 12.63 | 7.85 | 0.814 |
| 65              | 43 | 5.76 | 7.02 | 32 | 8.21 | 5.87 | 0.114 | 43 | 8.38 | 6.74 | 32 | 11.06 | 7.22 | 0.103 |
| 60              | 43 | 4.67 | 7.71 | 29 | 8.33 | 4.62 | 0.025 | 43 | 7.17 | 7.39 | 29 | 11.76 | 5.33 | 0.005 |
| 55              | 41 | 3.60 | 6.08 | 31 | 5.87 | 8.67 | 0.195 | 41 | 7.77 | 6.16 | 31 | 9.38 | 8.29 | 0.346 |
| 50              | 40 | 1.93 | 6.26 | 30 | 5.32 | 6.36 | 0.029 | 40 | 6.04 | 6.81 | 30 | 10.01 | 5.25 | 0.010 |
| 45              | 36 | −0.69 | 6.77 | 30 | 3.34 | 7.00 | 0.020 | 36 | 4.43 | 7.16 | 30 | 8.47 | 6.32 | 0.019 |
| 40              | 30 | −3.44 | 9.07 | 26 | 1.72 | 6.14 | 0.017 | 30 | 2.15 | 7.46 | 26 | 6.82 | 6.45 | 0.016 |

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in the stimulation intensity (from 20 dB SPL to 80 dB SPL, at 10-dB intervals) is reflected by a frequency-specific increase in the I/O emission, by 10 dB, 8 dB, and 5 dB for 2 kHz, 4 kHz, and 8 kHz, respectively [26]. In our study, statistically significant differences between smokers and non-smokers were observed at 1 kHz, 1.5 kHz, 2 kHz, and 3 kHz. Moreover, we found significant differences between male smokers and male non-smokers at 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, and 4 kHz, as well as between male and female smokers at 1 kHz, 2 kHz, and 5 kHz. Altogether, these findings suggest that smoking exerts particularly unfavorable effects on the cochlear OHC in men, but not in women. Importantly, we showed that the incidence SOAEs in smokers was significantly lower than in non-smokers. This new observation requires verification in future studies.

To the best of our knowledge, our study is the first to demonstrate sex-specific differences in CEOAE, DPOAE, and OAE responses of smokers. Using an objective method for otoacoustic emission analysis, we showed that the smoking-related alterations were more pronounced in men than in women. These sex-specific differences in otoacoustic emission levels might

Table 14 continued. DPOAE levels – I/O analysis in male smokers and male non-smokers.

| L2 level dB SPL | Male smokers | Male non-smokers | p | Male smokers | Male non-smokers | p |
|-----------------|--------------|------------------|---|--------------|------------------|---|
|                 | n | mean | SD | n | mean | SD | p | n | mean | SD | p |
| 4000 Hz DPOAE levels | 70 | 44 | 13.07 | 6.77 | 30 | 14.84 | 5.11 | 0.228 | 44 | 22.68 | 6.93 | 30 | 25.95 | 5.40 | 0.033 |
|                 | 65 | 44 | 11.84 | 7.18 | 30 | 13.70 | 5.12 | 0.227 | 44 | 21.05 | 7.24 | 30 | 23.71 | 4.50 | 0.078 |
|                 | 60 | 43 | 10.61 | 7.37 | 31 | 11.23 | 7.24 | 0.720 | 43 | 19.72 | 7.49 | 31 | 20.81 | 7.77 | 0.547 |
|                 | 55 | 42 | 9.20 | 8.56 | 31 | 9.94 | 7.31 | 0.700 | 42 | 18.21 | 7.96 | 31 | 18.97 | 7.30 | 0.678 |
|                 | 50 | 44 | 6.09 | 9.99 | 31 | 8.09 | 6.64 | 0.333 | 44 | 16.17 | 9.46 | 31 | 17.69 | 6.83 | 0.445 |
|                 | 45 | 43 | 4.41 | 11.15 | 31 | 5.62 | 7.40 | 0.341 | 43 | 13.21 | 10.03 | 31 | 15.45 | 7.62 | 0.300 |
| 5000 Hz DPOAE levels | 40 | 42 | 0.84 | 11.43 | 32 | 2.76 | 7.67 | 0.415 | 42 | 10.51 | 10.06 | 32 | 12.48 | 7.47 | 0.356 |
|                 | 70 | 43 | 12.76 | 8.53 | 32 | 13.56 | 8.61 | 0.691 | 43 | 21.97 | 7.99 | 32 | 24.26 | 8.25 | 0.227 |
|                 | 65 | 43 | 11.14 | 7.53 | 32 | 11.25 | 9.94 | 0.957 | 43 | 20.09 | 7.50 | 32 | 20.91 | 9.20 | 0.675 |
|                 | 60 | 44 | 9.43 | 8.43 | 32 | 10.38 | 8.61 | 0.631 | 44 | 18.12 | 8.00 | 32 | 19.69 | 8.46 | 0.413 |
|                 | 55 | 43 | 7.67 | 8.23 | 31 | 9.47 | 6.42 | 0.313 | 43 | 16.52 | 7.40 | 31 | 18.73 | 5.27 | 0.160 |
|                 | 50 | 43 | 4.60 | 9.43 | 32 | 5.48 | 9.93 | 0.699 | 43 | 14.65 | 7.89 | 32 | 15.65 | 9.17 | 0.614 |
|                 | 45 | 43 | 2.43 | 10.38 | 32 | 2.81 | 11.40 | 0.884 | 43 | 12.44 | 8.57 | 32 | 12.96 | 10.75 | 0.817 |
| 6000 Hz DPOAE levels | 40 | 42 | –1.00 | 11.57 | 31 | 1.00 | 8.67 | 0.421 | 42 | 9.18 | 9.45 | 31 | 10.94 | 7.08 | 0.387 |
|                 | 70 | 44 | 12.35 | 10.25 | 32 | 14.22 | 8.87 | 0.408 | 44 | 22.65 | 10.64 | 32 | 24.90 | 8.76 | 0.332 |
|                 | 65 | 42 | 11.75 | 8.10 | 30 | 13.36 | 8.64 | 0.420 | 42 | 21.18 | 7.72 | 30 | 22.99 | 8.57 | 0.352 |
|                 | 60 | 44 | 7.71 | 10.69 | 30 | 11.31 | 6.75 | 0.107 | 44 | 17.61 | 9.69 | 30 | 20.69 | 6.87 | 0.138 |
|                 | 55 | 43 | 5.73 | 10.40 | 32 | 6.76 | 10.18 | 0.670 | 43 | 15.62 | 9.31 | 32 | 15.87 | 10.15 | 0.911 |
|                 | 50 | 43 | 1.76 | 12.21 | 32 | 4.40 | 8.46 | 0.297 | 43 | 12.29 | 10.90 | 32 | 14.60 | 8.04 | 0.316 |
|                 | 45 | 42 | –2.10 | 13.28 | 32 | –0.07 | 9.98 | 0.472 | 42 | 8.59 | 11.32 | 32 | 10.48 | 9.44 | 0.446 |
| 6000 Hz SNR analysis | 40 | 38 | –5.92 | 13.34 | 31 | –4.95 | 12.25 | 0.754 | 38 | 5.13 | 11.00 | 31 | 6.37 | 10.34 | 0.634 |
Table 15. DPOAE levels – I/O analysis in female smokers and female non-smokers.

| L2 level | Female smokers | Female non-smokers | p       | Female smokers | Female non-smokers | p       |
|----------|----------------|--------------------|---------|----------------|--------------------|---------|
| dB SPL   | n mean SD      | n mean SD          |         | n mean SD      | n mean SD          |         |
|          | 1000 Hz DPOAE levels | 1000 Hz SNR analysis |         | 1500 Hz DPOAE levels | 1500 Hz SNR analysis |         |
| 70       | 42 9.03 6.38 49 9.57 5.27 | 0.658 42 12.13 5.53 49 13.33 5.81 0.320 |
| 65       | 41 8.06 6.77 49 6.73 5.83 | 0.320 41 10.90 4.90 49 10.73 5.57 0.880 |
| 60       | 41 7.69 6.69 49 6.46 5.63 | 0.346 41 10.54 5.75 49 10.60 6.02 0.957 |
| 55       | 41 6.56 6.29 46 5.13 5.94 | 0.279 41 10.52 5.03 46 10.12 4.60 0.695 |
| 50       | 39 4.66 6.75 45 2.72 8.19 | 0.244 39 10.01 4.94 45 8.63 8.20 0.362 |
| 45       | 39 2.48 7.07 42 2.40 5.44 | 0.952 39 7.62 5.25 42 8.41 5.54 0.513 |
| 40       | 34 –1.55 10.25 42 –2.25 9.33 | 0.757 34 4.39 8.71 42 4.77 8.11 0.844 |
|          | 1500 Hz DPOAE levels | 1500 Hz SNR analysis |         | 2000 Hz DPOAE levels | 2000 Hz SNR analysis |         |
| 70       | 41 13.45 7.84 49 13.26 5.40 | 0.889 41 17.77 8.15 49 20.45 6.05 0.077 |
| 65       | 41 12.68 7.28 48 12.27 5.10 | 0.754 41 16.93 7.42 48 18.13 5.88 0.399 |
| 60       | 42 11.07 7.73 47 11.03 5.28 | 0.974 42 15.42 6.75 47 16.87 5.84 0.279 |
| 55       | 42 9.09 9.08 49 8.01 8.83 | 0.566 42 14.37 7.95 49 14.21 7.82 0.934 |
| 50       | 41 7.75 6.67 49 6.05 7.18 | 0.251 41 12.92 5.93 49 12.65 6.69 0.841 |
| 45       | 40 4.54 8.95 49 4.20 7.44 | 0.845 40 10.55 6.65 49 11.62 7.12 0.468 |
| 40       | 34 2.10 10.57 49 1.72 7.26 | 0.849 34 7.94 7.86 49 10.05 6.46 0.184 |
|          | 2000 Hz DPOAE levels | 2000 Hz SNR analysis |         | 3000 Hz DPOAE levels | 3000 Hz SNR analysis |         |
| 70       | 42 13.20 5.72 50 11.38 5.47 | 0.123 42 21.49 6.43 50 20.54 6.22 0.475 |
| 65       | 42 12.33 5.72 50 10.68 5.44 | 0.160 42 19.40 5.76 50 19.42 5.81 0.988 |
| 60       | 42 10.60 6.06 50 9.59 5.50 | 0.406 42 18.10 5.87 50 18.15 6.22 0.968 |
| 55       | 42 8.66 6.27 50 7.68 5.50 | 0.425 42 16.23 6.12 50 16.72 5.63 0.691 |
| 50       | 41 6.70 6.31 49 5.58 5.82 | 0.383 41 14.96 6.06 49 14.91 5.22 0.966 |
| 45       | 41 4.27 6.70 49 2.03 8.98 | 0.192 41 12.81 5.11 49 12.19 7.80 0.659 |
| 40       | 38 2.19 6.70 48 –1.61 10.26 | 0.051 38 10.65 5.43 48 8.76 9.32 0.270 |
|          | 3000 Hz DPOAE levels | 3000 Hz SNR analysis |         |                   |                   |         |
Table 15 continued. DPOAE levels – I/O analysis in female smokers and female non-smokers.

| L2 level dB SPL | Female smokers | Female non-smokers | p | Female smokers | Female non-smokers | p |
|-----------------|----------------|--------------------|---|----------------|--------------------|---|
|                 | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  | mean | SD    | n  |
|                 |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |
| 4000 Hz DPOAE levels |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |
| 70              | 14.44 | 5.75 | 50 | 14.11 | 5.26 | 0.771 | 42 | 24.79 | 6.36 | 50 | 25.26 | 5.52 | 0.707 |
| 65              | 13.52 | 5.85 | 50 | 13.22 | 5.08 | 0.794 | 42 | 22.70 | 6.01 | 50 | 23.53 | 5.37 | 0.483 |
| 60              | 11.90 | 6.24 | 50 | 11.87 | 5.15 | 0.974 | 42 | 20.63 | 6.27 | 50 | 21.20 | 5.21 | 0.980 |
| 55              | 10.61 | 6.60 | 50 | 10.43 | 5.56 | 0.889 | 42 | 20.50 | 6.15 | 50 | 20.79 | 5.02 | 0.805 |
| 50              | 8.40  | 8.75 | 50 | 8.61  | 5.54 | 0.886 | 42 | 18.37 | 7.55 | 50 | 19.18 | 4.98 | 0.540 |
| 45              | 5.55  | 9.59 | 50 | 5.89  | 7.59 | 0.850 | 42 | 15.65 | 7.75 | 50 | 16.58 | 6.54 | 0.537 |
| 40              | 2.67  | 10.59 | 48 | 4.14  | 6.17 | 0.414 | 42 | 12.62 | 8.85 | 48 | 14.55 | 5.84 | 0.220 |
| 5000 Hz DPOAE levels |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |
| 70              | 15.52 | 7.48 | 50 | 14.77 | 6.51 | 0.611 | 42 | 25.57 | 7.95 | 50 | 25.47 | 6.95 | 0.042 |
| 65              | 13.63 | 7.49 | 50 | 12.62 | 7.27 | 0.513 | 42 | 22.58 | 6.69 | 50 | 22.38 | 6.20 | 0.883 |
| 60              | 12.35 | 7.21 | 50 | 11.14 | 8.86 | 0.478 | 42 | 21.80 | 6.58 | 50 | 21.18 | 7.87 | 0.688 |
| 55              | 9.92  | 7.66 | 50 | 9.45  | 7.64 | 0.770 | 42 | 19.66 | 6.22 | 50 | 19.41 | 6.13 | 0.848 |
| 50              | 7.44  | 9.21 | 50 | 7.10  | 8.19 | 0.853 | 42 | 17.00 | 7.20 | 50 | 17.11 | 7.03 | 0.942 |
| 45              | 4.03  | 10.65 | 48 | 5.42  | 8.20 | 0.480 | 42 | 14.50 | 8.44 | 48 | 15.84 | 6.67 | 0.397 |
| 40              | 0.66  | 12.41 | 49 | 3.36  | 6.92 | 0.196 | 41 | 10.76 | 10.43 | 49 | 13.62 | 6.50 | 0.117 |
| 6000 Hz DPOAE levels |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |      |       |    |
| 70              | 14.84 | 8.32 | 50 | 13.93 | 6.97 | 0.573 | 42 | 25.40 | 7.74 | 50 | 25.19 | 7.20 | 0.894 |
| 65              | 12.69 | 8.41 | 50 | 12.04 | 6.98 | 0.683 | 42 | 22.36 | 7.74 | 50 | 22.22 | 6.65 | 0.921 |
| 60              | 10.40 | 9.16 | 50 | 9.35  | 7.83 | 0.557 | 42 | 20.28 | 7.49 | 50 | 19.56 | 7.13 | 0.638 |
| 55              | 7.59  | 11.66 | 49 | 6.91  | 7.27 | 0.735 | 40 | 18.03 | 9.68 | 49 | 17.64 | 6.23 | 0.821 |
| 50              | 2.99  | 14.27 | 49 | 3.75  | 8.90 | 0.759 | 41 | 13.30 | 12.07 | 49 | 15.01 | 7.14 | 0.406 |
| 45              | 1.59  | 12.31 | 48 | 0.46  | 9.51 | 0.629 | 39 | 11.55 | 9.94 | 48 | 12.14 | 7.94 | 0.760 |
| 40              | −2.75 | 13.34 | 42 | −3.34 | 11.09 | 0.828 | 40 | 8.09  | 10.74 | 42 | 8.71  | 9.39 | 0.781 |

reflect the influence of genetic, hormonal, behavioral, and/or environmental factors.

Previous studies documented evident sex-specific differences in the CEOAE levels of infants and children. Cassidy and Ditty [36] showed that compared to male newborns, female newborns present with significantly higher CEOAE levels at 1.6 kHz, 2.4 kHz, 3.2 kHz, and 4.0 kHz. Also, Aidan et al. [37] demonstrated that mean CEOAE levels in female neonates are higher than in male neonates (22.1 dB SPL vs. 21.4 dB SPL). Interestingly, the same study documented significant differences in the CEOAE levels recorded in the right and left ear (22.4 dB SPL vs. 21 dB SPL) [37]. In another study, 12-year-old girls were shown to present with significantly higher CEOAE levels than their male peers [38]. However, in contrast to Aidan et al. [37], the authors of this study did not observe a bilateral asymmetry in CEOAE levels [38]. Although we did not reveal sex-specific differences in the otoacoustic emission levels of non-smokers, it cannot be excluded that men present with a genetically determined (i.e., sex hormone-independent) greater susceptibility of cochlear OHCs to the ototoxic components of tobacco smoke.
The results of experimental studies point to a potential protective effect of female sex hormones as an explanation of sex-specific differences in hearing. Estrogens, 17α-estradiol, 17β-estradiol, estrone, and estriol were shown to protect against gentamicin-induced outer hair cell death; the effect of 17β-estradiol is mediated by estrogen receptor (ER) [39]. Interestingly, the expression of estrogen receptors ERα and ERβ in the inner ear (i.e., in the nuclei of stria vascularis, outer and inner hair cells, spiral ganglion cells, vestibular ganglion cells, and vestibular dark cells) is known to decrease with age [40]. These findings are consistent with the results of clinical studies. For example, Kilicdag et al. [21] demonstrated that estrogen therapy may protect against hearing loss in aging postmenopausal women. Taking this evidence into account, it can be hypothesized that female sex hormones may also protect against tobacco-smoke-induced hearing impairment.

Behavioral factors should also be considered as a potential cause of sex-specific differences in susceptibility to tobacco-related hearing loss. Men not only smoke more, but also use stronger cigarettes, as well as other stimulants [41–43]. Our study included 21 women and 22 men, who smoked at least 15 cigarettes per day for at least 7 years. We did not compare, however, the total number of cigarettes smoked by the female and male participants. Consequently, our male smokers might be exposed to tobacco smoke more often and for a longer period of time than female smokers. Finally, the influence of environmental chemical ototoxins should be taken into account as a confounding factor resulting in greater impairment of hearing in our male smokers [44].

To summarize, tobacco smoke likely induces an array of subclinical changes in the organ of hearing, especially in males. Therefore, appropriate strategies preventing resultant hearing loss should be implemented before it will manifest clinically and impair patient functioning. These strategies should be adjusted for these documented sex-specific differences in susceptibility to tobacco smoke-induced hearing impairment.

Conclusions

This study showed that smoking induces an array of subclinical changes in the organ of hearing. Specifically, while it does not modulate the hearing threshold determined with PTA at low, moderate, and high frequencies, it causes a significant decrease in OAE levels, but only in males. Furthermore, smoking impairs the active and passive mechanisms of male cochlea.

Disclaimers

No conflicts of interest is noted. No relationships with industry to be noted.

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