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Effects of Primary and Secondary Cigarette Smoke on Auditory Function: A Systematic Review

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THE EFFECT OF PRIMARY AND SECONDARY CIGARETTE SMOKE ON AUDITORY FUNCTION: A SYSTEMATIC REVIEW

by

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A capstone research project submitted to the Graduate Faculty in Audiology in partial fulfillment of the requirements for the degree of Doctor of Audiology, The City University of New York

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ABSTRACT

THE EFFECT OF PRIMARY AND SECONDARY CIGARETTE SMOKE ON AUDITORY FUNCTION: A SYSTEMATIC REVIEW

by

HILARY MCMANUS

Advisor: Carol Silverman, Ph.D., M.P.H.

Objective: The goal of this paper was to systematically review literature in order to investigate the effects of active and passive cigarette smoke on auditory function when assessing outcome measures including pure tone audiometry, otoacoustic emissions, high-frequency audiometry, and auditory evoked potentials.

Methods: A comprehensive search using the Medline Complete database was conducted to identify relevant studies published after 2005. Inclusion criteria included the use of pure tone audiometry, high-frequency audiometry, otoacoustic emissions, and/or auditory evoked potentials to examine the effect of primary or secondary cigarette smoke. Studies involving noise exposure or other confounding factors were excluded.

Results: A total of 19 studies were selected for review based on their research design, publication date, and inclusion criteria. All included studies achieved a significant negative correlation between cigarette smoking and auditory function for both active and passive smokers. Additionally, a dose effect was noted as poorer outcomes were achieved as smoking behavior, such as packs per year or years smoking, increased.

Discussion: Significant effects of smoking on auditory function were noted across outcome measures suggesting a negative effect across levels of the auditory system. Effects on auditory function were noted even in those who had quit smoking suggesting long term side effects of the behavior on auditory function. A dose effect was noted with negative effects increasing across groups from never smokers, to passive smokers, to current smokers. The dose effect was further stratified within the current smoking group as negative effects increased with an increase in smoking behavior.

Conclusion: Smoking behavior should be avoided due to its effects on auditory function, as well as the myriad of other heavily researched deleterious side effects. It would be advantageous to include the question of smoking behavior in an audiologic evaluation intake form. This question should also include systematic exposure to secondhand smoke. Additionally, smoking cessation can be recommended to reduce effects on auditory function.

Key Words: “smoking,” “hearing loss,” “cigarette,” “auditory evoked potentials,” “otoacoustic emissions,” “audiometry.”

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To my grandparents, John Carrozza and the late Patricia Carrozza, I could not have completed this journey without you. Thank you to my grandmother for inspiring my passion for this topic. She is greatly missed and will always remain in my thoughts. Thank you to my grandfather for his support and guidance that he has so selflessly given in many ways. This capstone is dedicated to you.

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INTRODUCTION

Worldwide, there are roughly 1 billion (967 million) smokers aged 15 years of age and older (Ng, Freeman, & Fleming, 2014). Of these 1 billion smokers, 31% are male and 6.1% are female (Lisowska, Jochem, Gierlotka, Misiotek, & Scierski, 2017). As a result, 88 million adults and children of at least three years of age are exposed to secondhand smoke (SHS) (Centers for Disease Control, 2010). By 2025, an estimated 1.5 – 1.9 billion people will be smokers (Shafey, Dolwick, & Guindon, 2003). According to the Centers for Disease Control (CDC), smoking prevalence is slightly less than 15% in the United States, with 15.8% of all males and 12.2% of all females reporting smoking "some days" or "every day." Of these, 75% report smoking every day. In terms of age groups, 10.4% of adults age 18 – 24 years, 16.1% of adults age 25 – 44 years, 16.5% of those age 45 – 64 years, and 8.2% of those over 65 years, report current smoking either "every day" or "some days" (CDC, 2017). Additionally, of those 65 years and older, 80% have at least one chronic condition, which smoking often exacerbates (Fried, Freedman, Endres, & Wasik, 1997). Hearing loss itself is ranked third among chronic health conditions in adults age 65 years and older (Collins, 1997). It is a major public health concern with a prevalence of 33% in adults 65 or more years of age (Davila et al., 2009).

Tobacco use is the leading cause of preventable deaths worldwide (World Health Organization, 2003). In the United States, cigarette smoking causes 480,000 deaths each year and increases the risk of death from all causes across genders. Smokers are at a greater risk for a myriad of health conditions such as bacterial respiratory infections, acute and chronic viral diseases, oral, laryngeal, esophageal, pancreatic, renal, and bladder cancer, circulatory disease such as arteriosclerosis, aortic aneurism, stroke, and multiple other organ disorders. Specifically, smoking increases the risk of coronary heart disease and strokes by 2 – 4 times, of lung cancer in

men by 25 times, and of lung cancer in women by 25.7 times. Smoking also increases both the risk and severity of Chronic Obstructive Pulmonary Disease (COPD) with smokers being 12 to 13 times more likely to die from COPD than non-smokers (U.S. Dept. of Health and Human Services, 2010; 2014). Other smoking effects include reduced fertility, bone health, tooth and gum health; increased risk of cataracts, age-related macular degeneration, type 2 diabetes, rheumatoid arthritis; and general adverse effects including inflammation and decreased immune function (U.S. Department of Health and Human Services, 2001; 2010; 2014). Smokers not only exhibit poorer vascular and respiratory health, but also present with poorer cognitive health included an increased risk for dementia, with many showing reduced cognitive performance later in life (Chang, Ho, Wang, Gentleman, & Ng, 2014; Mons, Schottker, Muller, Kliegal, & Brenner, 2013).

Cigarette smoking is the primary method of nicotine intake with each cigarette containing 9 – 13 mg of nicotine (Kozlowski, Henningfield, & Brigham, 2001). Nicotine is rapidly absorbed by nicotinic receptors in the nervous system and can lead to physiologic, cognitive, and sensory effects (Stratton, Shetty, Wallace, & Bondurant, 2001). Additionally, cigarette smoke contains more than 4500 complex chemicals including carbon monoxide (CO), carbon dioxide, mercury, and arsenic (Gopal, Herrington, & Pearce, 2009; Cruickshanks et al., 1998). The effects of such toxicity are greatly related to number of cigarettes smoked, age of smoking onset, degree of inhalation, and the different characteristics of cigarette brands such as tar and nicotine content (Peto, 1986). Smoking simultaneously increases the need for oxygen while decreasing the amount of oxygen reaching the bloodstream, thus minimizing oxygen available to vital organs (Moliterno et al., 1994). While it is not yet known how severely these effects impact the auditory

system, smoking is related to lower blood oxygen levels, increased blood viscosity, vascular obstruction, and possible ototoxicity (Paschoal & Azevedo, 2009).

Specific to auditory function, the inner ear is dependent on adequate blood supply and thus may be susceptible to alterations in blood flow caused by tobacco. These alterations include peripheral vascular changes, such as increased blood viscosity and reduced oxygen availability. As a result, smoking is known to affect cochlear circulation, inducing vasospasm and arteriosclerosis in the cochlear blood vessels. Not only does smoking adversely affect cochlear circulation, but also it adversely affects the cardiovascular system; in turn, this effect on the latter leads to an increased risk of diabetes, which can result in hearing loss. Nicotine in tobacco smoke has a direct ototoxic effect on cochlear hair cells. Carbon monoxide in tobacco smoke can cause a rise in carboxyhaemoglobin levels in smokers, which can reduce the passage of oxygen for the Organ of Corti. As noted previously, smoking increases the need for oxygen in the human body and the rise in carboxyhaemoglobin levels results in a reduction of available oxygen. Even exposure to SHS can damage the inner ear due to hypoxemia or direct injury by nicotine or other chemicals (Lalwani, Liu, & Weitzman, 2011; Talaat, Metwaly, Khafagy, & Abdelraouf, 2013). Some researchers have suggested that smokers who are older than 40 years of age have an increased prevalence of hearing loss, reflecting an additive effect of the normal aging process and the aforementioned effects of smoking on the cochlea. Age-related degenerative changes can also affect the vascular structures of the cochlea, just as tobacco does (Chang, Ryou, Jun, Hwang, Song, & Chae 2016; Ferrite & Santana, 2005).

Nomura, Nakao, and Morimoto (2005) conducted a meta-analysis examining the effect of smoking on pure-tone thresholds. In contrast with the current review, those investigators included studies on participants with a history of noise exposure in their meta-analysis. They also

limited their search to studies utilizing pure-tone average alone as their outcome measure. Their review revealed a positive association between smoking and pure-tone average. Research findings reveal significant relative risk for hearing loss from hearing loss in current smokers: relative risk was 1.33 (95% CI: 1.24, 1.44) based on cross-sectional studies; 1.97 (95% CI: 1.44, 2.70) based on cohort studies; and 2.89 (95% CI: 2.26, 3.70) based on case-control studies. Furthermore, relative risk also was significant for hearing loss in ex-smokers: relative risk was 1.17 (95% CI: 1.03, 1.33) based on cross-sectional studies; and 1.83 (95% CI: 1.43, 2.35) based on case-control studies. Although the investigators extracted data on age, noise exposure, and smoking history, this association was dependent on the adjustment for confounding factors such as age, noise exposure, and history of ear disorders. The purpose of this study was to conduct a systematic review of studies on smoking and hearing loss which utilized pure tone thresholds in the conventional range, ultra high-frequency thresholds, otoacoustic emissions (OAE) and auditory evoked potentials (AEPs) published since the aforementioned meta-analysis.

METHODS

The Medline Complete online database was searched. Search filters included peer-reviewed journals as well as articles published after 2005. The main search terms utilized were "smoking," and "hearing loss." Supplementary search terms, such as, "cigarettes," "passive smoking," "smoke exposure," and "auditory evoked potentials" were utilized to find additional studies for inclusion. This initial search yielded a total of 344 studies. As an existing systematic review assessed articles prior to 2005, the present review focused on those published in the years following 2005.

Studies were excluded if they involved concurrent effects of smoking and noise exposure or if the subjects included infants or children. This resulted in the exclusion of 318 studies. Subsequently applied exclusion criteria were animal studies or studies on individuals with schizophrenia and/or major depressive disorder or alcoholism; and studies on middle-ear pathologies and surgical outcomes resulting in the exclusion of 297 studies. Two studies originally published in the Georgian Medical news were excluded due to ambiguity of writing style and reporting of results. These exclusion criteria resulted in the 19 studies evaluated in this systematic review. Data extracted from the included studies involved conventional and ultra high-frequency pure-tone thresholds, otoacoustic emissions (OAEs) and AEPs.

RESULTS

Of the 19 studies evaluated, 89% (17) employed a descriptive, case-control research design, and 11% (2) employed a descriptive design whereby the characteristics of a single group of smokers or individuals exposed to secondhand smoke (SHS) are described. The majority of 19 studies (74%) were based on a sample size of at least 30 (Guney, Genc, Kutlu, & Ilhan, 2009; Gupta, Sood, Atreja, & Agarwal, 2008; Kumar, Gulati, Singhal, Hasan, & Khan, 2013; Lisowska, Jochem, Gierlotka, Misiotek, & Scierski, 2017; Ohgami Kondo, & Kato, 2011; Oliveira & Lima, 2009; Paschoal & Azevedo, 2009; Prabhu, Varma, Dutta, Kumar, & Goyal, 2017; Ramkissoon & Chambers, 2008; Ramkissoon & Cole, 2011; Sekher, Sinha, & Jha, 2017; Sumit et al., 2015), with the remainder (26%) based on a sample size of less than 30 (Gopal, Herrington, & Pearce, 2009; Negley, Katbamna, Crumpton, & Lawson, 2007). Of the 14 large-sample studies, 2 (14%) were population-based. Chang et al. (2016), drew participants from the Korea National Health and Nutrition Examination Survey (KNHANES). The KNHANES is an ongoing population study that began in 1998, with individuals who participated from 2010 – 2012 included in the Chang et al. study. Fabry et al. (2011) drew participants from the U.S. National Health and Nutrition Examination Survey (NHANES) who completed audiometric testing, provided complete smoking and medical histories, and who had a valid recorded serum cotinine value.

Of the 19 studies, 15 (79%) compared only 2 groups: smokers versus non-smokers; 1 (5%) involved only current smokers; 1 (5%) included a passive smoking group (those exposed to SHS) along with groups of smokers and nonsmokers; 1 (6%) involved only a passive smoking group; and 1 (5%) study compared smokers, non-smokers, and those who had quit smoking in the past. Of the 19 studies, 17 (90%) studies included non-smokers. Of these 17 studies, 3 (18%)

included past smokers, or those who quit smoking, in the non-smoking group. Of the 19 studies, 16 (84%) included groups matched for age while the remaining 3 (16%) separated groups into older and younger participants.

In terms of the quantification of smoke exposure, all studies subjectively assessed smoke exposure by self-reported responses to either a single question or multiple questions on smoking status. The questionnaires elicited general health information included in medical records or self-reported basic history involving smoking status, packs/cigarettes per day, frequency of smoking, and number of years as a smoker. Ohgami et al. (2011) also employed the Brinkman Index (BI) to examine the frequency or degree of smoking in the participants. The BI represents the number of cigarettes smoked per day multiplied by the number of years smoking (Brinkman & Coates, 1963). All the individuals in their non-smoking group had a BI of 0, whereas those in the smoking group all were classified as "light-smokers" with BI scores between 12 and 60. One study used the Global Initiative for chronic obstructive Lung Disease (GOLD) guidelines to diagnosis Chronic Obstructive Pulmonary Disease (COPD) (Gupta et al., 2008). The GOLD guidelines outline the key indicators of a COPD diagnosis, including dyspnea that is progressive and persistent, chronic cough, chronic sputum production, a history of risk factors, including but not limited to genetic factors, tobacco smoke, and occupational dusts or vapors, as well as a family history of COPD and/or childhood factors including low birth weight and childhood respiratory infections These guidelines also characterize the severity of COPD on a four tier scale (ABCD) (GOLD, 2019).

Of the 19 total studies, only 5 (26%) additionally used objective measures of smoke exposure (Fabry et al., 2011; Ramkissoon & Cole, 2011). Gopal et al. (2009) measured breath carbon monoxide (CO) levels to confirm the current smoking status of study participants. A

breath CO monitor, used to measure the concentration of CO in the individual's breath, allows for the quick and accurate assessment of the presence of CO. Fabry et al. used serum cotinine levels to determine the level of secondhand smoke exposure. Cotinine, a biomarker of exposure to tobacco in both active and passive smokers, or those exposed to tobacco smoke, is the primary metabolite of nicotine (Benowitz, 1996). As the lower limit of detection of serum cotinine is 0.50 ng/mL and the suggested level indicating current smokers is 3 ng/mL or above, only individuals with levels within this range (0.50 – 3 ng/mL) were included. Ramkissoon and Cole also utilized cotinine levels to determine smoking status. Additionally, they tested the urine of participants for the presence of this biomarker, as well as for the presence of nicotine. The self-reports of smoking status and the biochemical results were in 100% agreement. Mobascher et al. (2009) utilized carboxyhemoglobin (COHb), a complex of carbon monoxide that forms in red blood cells when carbon monoxide is inhaled, as an objective measure of smoke exposure (Thaniyavarn & Eiger, 2014).

Outcome measures included conventional pure-tone thresholds (250 – 8,000 Hz), ultra high-frequency thresholds, OAEs, and latencies and amplitudes of AEPs. Of the 19 studies, the majority 14 (74%) assessed conventional pure-tone thresholds; 6 (32%) evaluated extended or ultra high-frequency pure-tone thresholds; 6 (32%) examined OAEs; and 6 (32%) evaluated the AEPs. The percentages total more than 100% as some studies evaluated more than one type of outcome measure. Tables 1 through 4 shows the characteristics of the studies on effects of smoking on conventional pure-tone thresholds, ultra high-frequency pure-tone thresholds, OAEs, and the AEPs, respectively.

Table 1

Characteristics of Studies on Conventional Pure-Tone Thresholds

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Chang et al (2016)	12,935	South Korean individuals aged 19+ yrs[a]: current smoking group (n= 3,374), passive smoking group (n= 2,792), non-smoking group (n= 6,769)	Smoking group - currently smoke; passive smoking group - exposed to cigarette fumes daily at home and/or work; non-smoking group - never smoked and never exposed to cigarettes	Presence of unilateral hearing impairment	Chi-square ($\chi 2$) testing, odds ratio with 95% CI (adjustments for age, sex, work related noise exposure, diabetes, hypertension, depression, stress, and regular exercise) and linear regression analysis	Descriptive case control
Fabry et al (2011)	5147	Subject population aged 20 - 69 yrs who were not current smokers but SHS exposed	Secondhand smoke expose - serum contine level at or above 0.050 ng/mL	Current smokers (based upon Q[b] and cotinine levels above 3 ng/mL)	Multivariate logistic regression	Descriptive
Gopal et al (2009)	16	Adult male smokers with no hx[c] of HL and hx of smoking of 4 yrs on average and a mean use of 17 cigarettes per day aged 18 – 24	Current smokers	Hearing loss and outer/middle ear problems, peripheral abnormalities ruled out via otoscopic examination	Linear regression and effect size (via lmg statistics)	Descriptive (predictive)

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Kumar et al (2013)	148	108 male smokers aged 20 - 60 yrs (mean age=37 yrs) age-matched non-smokers (mean age=41 yrs)	Smokers were previous or current smokers	Hx of ototoxic drugs, diabetes, hypertension, hearing loss, severe or frequent ear infections, ear surgery, head injury, noise exposure, family hx of hearing loss	Unreported	Descriptive Case Control
Lisowska et al (2017)	84	41 non-smokers (mean age=33 yrs) and 43 smokers (mean age=35 yrs) aged 25-45. Total of 46 females and 38 males in Poland.	Smoking for 7+ yrs and 15+ cigarettes/day	Hx of audiological impairment, abnormal otoscopic examination, ear problems, conductive hearing loss, noise exposure, ototoxic drugs, head injury, family history of hearing loss; current disorders of cholesterol metabolism, chronic metabolic disordes, hypertension, CNS[d] disorders, abnormal BMI[e], and other acute or chronic systemic conditions	Shapiro-Wilk test, Student t-test (CEOAE[f]), Mann-Whitney-U-test, Bonferroni correction (PTT[g] and DPOAE[h]).	Descriptive case control

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Negley et al (2007)	24	12 smokers and 12 non-smokers aged 20-30 yrs	In smokers: hx of 5-8 years of smoking	Noise exposure or ear diseases, abnormal middle-ear pathology based on tympanometric screen	3 factor ANOVA[i]	Descriptive case control
Ohgami et al (2011)	51	Smoking and non-smoking males aged 21 - 23 yrs	Light smokers re: Brinkman Index (BI) - cigarettes/day X number of yrs smoked	NA	Mann-Whitney U test, binary logistic regression analysis	Descriptive case control
Oliveira & Lima (2009)	60	30 male smokers aged 18 -40 yrs (mean age=31 ± 6 yrs); 30 male age-matched non-smokers (mean age=28 ± 6 yrs)	Smokers were active smokers for 5+ yrs	Hx of ear disorders, tinnitus, dizziness, hearing loss, prior ear surgery, otoscopic alterations, work-related noise exposure, hypertension, diabetes; neurologic disease; PTT > 25 dB HL at any 1+ frequency; illiteracy; visual disorders	ANOVA	Descriptive Case Control
Paschoal & Azevedo (2009)	144	72 smokers and 72 non-smokers paired by gender and age (20 - 31 yrs)	In smokers: current smokers who smoked 5+ cigarettes/day for 1+ yrs	Former smokers; presence of inner or middle ear disorders, metabolic disordrs, hormonal disorders, or	Student t-test, Mann-Whitney U test, two ratio equality tests, and the Spearman test	Descriptive case control

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
				noise-induced or drug-induced HL		
Prabhu et al (2017)	50	25 male smokers and 25 male non-smokers aged 18-40[2] yrs in India	Current smokers who have smoked for 1+ yr; PTTs ≤ 25 dB HL (.25l - 6k Hz)	Otological hx of noise exposure, ototoxic drugs, diabetes, family hx of hearing loss; abnormal middle-ear function	ANOVA, MANOVA[j] (UHF[k]), post-hoc Sidak Test, independent t-test, correlation	Descriptive case control
Ramkissoon & Cole (2011)	170	61 males, 109 female; 98 non-smokers and 72 smokers; younger group n= 80, age 19 - 30 (mean age 24±3.9) and older group n=90, age 45+ mean age 62±9.3); non-smokers included those who quit smoking 3+ years prior	Current smokers - self-report confirmed by biochemical urine testing; non-smokers - never smoked or quit at least 3 years prior	Poor overall health, alcohol or drug dependency, mental illness, or neurological disease	Prevalence, sensitivity, specificity, predictive value and conditional probability	Descriptive Case Control
Rogha et al. (2015)	32	Men aged 20 - 60; smoking group and non-smoking group matched for age and gender		No history of ototoxic drug use, diabetes, hypertension, hyperlipidemia, hypothyroidism, ear infection/surgeries, occupational noise exposure, outer and/or middle ear disease, unilateral or conductive hearing loss	T-test, ANOVA	Descriptive case control

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Sekher et al (2017)	120	60 smokers and 60 non-smokers aged 20-60 yrs	In smokers: currently smoke	Chronic supprative otitis media and other middle and internal ear pathology; hx of ototoxic drugs, working in a noisy environment, congenital anomalies, and other systemic diseases such as diabetes and viral infection causing sudden SNHL[l] or unilateral SNHL	Descriptive statistics (percentages) only	Descriptive case control
Sumit et al (2015)	184	90 male smokers (mean age 39 ±12 yrs) and 94 male non-smokers (mean age 36 ± 12 yrs) aged 18-60 yrs in Bagladesh; groups did not differ on mean age or BMI	Age 18 - 60 yrs	Hx of alcohol drinking habit, use of portable music player with earphone, middle-ear disease; current illness	$\chi 2$ testing, regression analysis	Descriptive case control

[a]Years
[b]Questionnaire
[c]History
[d]Central nervous system
[e]Basal mass index
[f]Click evoked otoacoustic emissions
[g]Pure-tone threshold
[h]Distortion product otoacoustic emissions
[i]Analysis of variance
[j]Multivariate analysis of variance
[k]Ultra high frequency
[l]Sensorineural hearing loss

Table 2

Characteristics of Studies on Effects of Smoking on the Ultra High-Frequency Pure-Tone Thresholds

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Lisowska et al (2017)	84	41 non-smokers (mean age=33 yrs) and 43 smokers (mean age=35 yrs[a]) aged 25-45. Total of 46 females and 38 males in Poland.	Smoking for 7+ yrs and 15+ cigarettes/day	Hx[b] of audiological impairment, abnormal otoscopic examination, ear problems, conductive hearing loss, noise exposure, ototoxic drugs, head injury, family history of hearing loss; current disorders of cholesterol metabolism, chronic metabolic disordes, hypertension, CNS[c] disorders, abnormal BMI[d], and other acute or chronic systemic conditions	Shapiro-Wilk test, Student t-test (CEOAE[e]), Mann-Whitney-U-test, Bonferroni correction (PTT[f] and DPOAE[g]).	Descriptive case control
Negley et al (2007)	24	12 smokers and 12 non-smokers aged 20-30 yrs	In smokers: hx of 5-8 yrs of smoking	Noise exposure or ear diseases, abnormal middle-ear pathology based on tympanometric screening	3 factor ANOVA[h],	Descriptive case control
Ohgami et al (2011)	51	Smoking and non-smoking males aged 21 - 23 yrs	Light smokers re: Brinkman Index (BI) - cigarettes/day X number of yrs smoked	NA	Mann-Whitney U test, binary logistic regression analysis	Descriptive case control

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Oliveira & Lima (2009)	60	30 male smokers aged 18 -40 yrs (mean age=31 ± 6 yrs); 30 male age-matched non-smokers (mean age=28 ± 6 yrs)	Smokers were active smokers for 5+ yrs	Hx of ear disorders, tinnitus, dizziness, hearing loss, prior ear surgery, otoscopic alterations, work-related noise exposure, hypertension, diabetes; neurologic disease; PTT > 25 dB HL at any 1+ frequency; illiteracy; visual disorders	ANOVA	Descriptive Case Control
Paschoal & Azevedo (2009)	144	72 smokers and 72 non-smokers paired by gender and age (20 - 31 yrs)	In smokers: current smokers who smoked 5+ cigarettes/day for 1+ yrs	Former smokers; presence of inner or middle ear disorders, metabolic disordrs, hormonal disorders, or noise-induced or drug-induced HL	Student t-test, Mann-Whitney U test, two ratio equality tests, and the Spearman test	Descriptive case control
Prabhu et al (2017)	50	25 male smokers and 25 male non-smokers aged 18-40 yrs in India	Current smokers who have smoked for 1+ yr; PTTs ≤ 25 dB HL (.25l - 6k Hz)	Otological hx of noise exposure, ototoxic drugs, diabetes, family hx of hearing loss; abnormal middle-ear function	ANOVA, MANOVA[i] (UHF[j]), post-hoc Sidak Test, independent t-test, correlation	Descriptive case control
Rogha et al. (2015)	32	Men aged 20 - 60; smoking group and non-smoking group matched for age and gender		No hx of ototoxic drug use, diabetes, hypertension, hyperlipidemia, hypothyroidism, ear infection/surgeries, occupational noise exposure, outer and/or middle ear disease, unilateral or conductive hearing loss	T-test; ANOVA	Descriptive case control

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Sumit et al (2015)	184	90 male smokers (mean age 39 ±12 yrs) and 94 male non-smokers (mean age 36 ± 12 yrs) aged 18-60 yrs in Bagladesh; groups did not differ on mean age or BMI	Age 18 - 60 years	Hx of alcohol drinking habit, use of portable music player with earphone, middle-ear disease; current illness	$\chi 2$ testing, regression analysis	Descriptive case control

[a]Years
[b]History
[c]Central nervous system
[d]Basal mass index
[e]Click evoked otoacoustic emissions
[f]Pure-tone threshold
[g]Distortion product otoacoustic emissions
[h]Analysis of variance
[i]Multivariate analysis of variance
[j]Ultra high frequency

Table 3

Characteristics of Studies on Effect of Smoking on OAEs

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Gopal et al (2009)	16	Adult male smokers with no history of HL and hx[b] of smoking of 4 yrs[a] on average and a mean use of 17 cigarettes per day aged 18 - 24	Current smokers	Hearing loss and outer/middle ear problems, peripheral abnormalities ruled out via otoscopic examination	Linear regression and effect size (via lmg statistics)	Descriptive (predictive)
Lisowska et al (2017)	84	41 non-smokers (mean age=33 yrs) and 43 smokers (mean age=35 yrs) aged 25-45. Total of 46 females and 38 males in Poland.	Smoking for 7+ yrs and 15+ cigarettes/day	Hx of audiological impairment, abnormal otoscopic examination, ear problems, conductive hearing loss, noise exposure, ototoxic drugs, head injury, family history of hearing loss; current disorders of cholesterol metabolism, chronic metabolic disordes, hypertension, CNS[c] disorders, abnormal BMI[d], and other acute or chronic systemic conditions	Shapiro-Wilk test, Student t-test (CEOAE[e]), Mann-Whitney-U-test, Bonferroni correction (PTT[f] and DPOAE[g]).	Descriptive case control
Negley et al (2007)	24	12 smokers and 12 non-smokers aged 20-30 yrs	In smokers: hx of 5-8 years of smoking	Noise exposure or ear diseases, abnormal middle-ear pathology based on tympanometric screening	3 factor ANOVA[h]	Descriptive case control

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Paschoal & Azevedo (2009)	144	72 smokers and 72 non-smokers paired by gender and age (20 - 31 yrs)	In smokers: current smokers who smoked 5+ cigarettes/day for 1+ yrs	Former smokers; presence of inner or middle ear disorders, metabolic disordrs, hormonal disorders, or noise-induced or drug-induced HL	Student t-test, Mann-Whitney U test, two ratio equality tests, and the Spearman test	Descriptive case control
Prabhu et al (2017)	50	25 male smokers and 25 male non-smokers aged 18-40 yrs in India	Current smokers who have smoked for 1+ yr; PTT $\leq$ 25 dB HL (.25l - 6k Hz)	Otological hx of noise exposure, ototoxic drugs, diabetes, family hx of hearing loss; abnormal middle-ear function	ANOVA, MANOVA[i] (UHF[j]), post-hoc Sidak Test, independent t-test, correlation	Descriptive case control
Rogha et al. (2015)	32	Men aged 20 - 60; smoking group and non-smoking group matched for age and gender		No history of ototoxic drug use, diabetes, hypertension, hyperlipidemia, hypothyroidism, ear infection/surgeries, occupational noise exposure, outer and/or middle ear disease, unilateral or conductive hearing loss	T-test, ANOVA	Descriptive case control

[a]Years
[b]History
[c]Central nervous system
[d]Basal mass index
[e]Click evoked otoacoustic emissions
[f]Pure-tone threshold
[g]Distortion product otoacoustic emissions
[h]Analysis of variance
[i]Multivariate analysis of variance
[j]Ultra high frequency

Table 4

Characteristics of Effects of Smoking on the AEPs

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Gopal et al (2009)	16	Adult male smokers with no history of HL and hx[b] of smoking of 4 yrs[a] on average and a mean use of 17 cigarettes per day aged 18 - 242	Current smokers	Hearing loss and outer/middle ear problems, peripheral abnormalities ruled out via otoscopic examination	Linear regression and effect size (via lmg statistics)	Descriptive (predictive)
Guney et al (2009)	64	32 male and female smokers and 32 age, gender and education level matched healthy individuals who had never smoked	Smokers smoked 15+ cigarettes/day by inhalation for 12+ yrs, all participants right-handed	Lifetime hx of major medical disorder (neurological, hepatic, or cardiovascular); head injury with loss of consciousness; seizures; sedative, barbiturate, alocohol or cocaine abuse or dependence; uncorrected auditory or visual impairment; current psycoactive medication use; women currently in the menstration phase of the menstrual cycle	Independent sample t-test and Pearson's correlation coefficient	Descriptive case control
Gupta et al (2008)	80	40 male smokers with stable COPD[i] with a duration of symptoms of 5+ yrs and 40 male aged-matched healthy controls 40+ yrs	Smokers: COPD patients with irreversible/partially reversible obstruction of airflow, stable course of disease with regular follow up in the preceding yr, and no hospitilizations related to COPD in the prior 6 months	Smokers: +clinical evidence of neurological deficit or neuropathy, concomitant diabetes, alcoholism, uremia, cystic fibrosis, sarcoidosis, leprosy, malignancy, hereditary disorders involving peripheral nerves; hx of neurotoxic drug use or traumatic lesion to the brainstem. Controls: hx of smoking or risk factor for neuropathy.	Independent sample t-test, Pearson's correlation	Descriptive case control

Study	Size (N)	Participants	Inclusion Criteria	Exclusion Criteria	Statistical Analysis	Type of Study
Jawinski et al (2016)	1739	Current (n=136), ex- (n=272), and never smokers (n=468) age 40 - 79 yrs; participants matched on sex, age, alcohol and caffeine consumption, and socioeconomic status; non-smokers included those with no 6 month history of 5+ cigarettes per week	Individuals from an existing study with sufficient EEG[e] assessment; data on socioeconomic status, tobacco use, alcohol and caffeine consumption, and hearing threshold levels	Current psychiatric disorder or intake of psychotropic medication; hx of major neurological disorder, or being a cigar, cigarillo, stogie, or pipe smoker; moderate or worse HL (>55 dB HL)	Repeated measures ANCOVA[f] with sex and age as covariates	Descriptive case control
Mobascher et al (2009)	1318	German light smokers (n=325; mean age=36 yrs), heavy smokers (n=271; mean age=41 yrs), or never smokers (n=722; mean age=35 yrs) aged 18-65 yrs (mean age=37 yrs)	Aged 18-65 yrs, current smoker with 7+ cigarettes per week/one per day; paticipant's grandparents born in germany; fluent German speakers	Former smokers, alcohol or substance abuse in the past 6 months; psychiatric diagnosis in the past 6 months; non-german origin; non-fluent in German; serious impairments of hearing or vision; pregnany; CNS[g]-related medication within 6 months; neurological illness	ANCOVA with P300 GFP[h] as dependent variable and smoking status, gender, and study site as independent variable. Age, years of education, alcohol use served as covariates	Descriptive case control
Ramkisson & Chambers (2008)	40	Younger non-smokers (n=10), younger smokers (n=10), mean age=25 yrs; older non-smokers (n=10) and older smokers (n=10), mean age= 61 yrs) ; included past smokers in non-smoking groups	Younger group: age 19-30 yrs; Older group; age 55-81 yrs. Smokers + on biochemical urine analysis; non-smokers negative on biochemical urine analysis	Alcohol or drug dependency, mental illness, neurological disease, significant HL, MLR[c] contaminated by post-auricular muscle reflex, mismatched between urine analysis and self reported smoking status	MANOVA[d]	Descriptive case control

[a]Years
[b]History
[c]Middle Latency Response

[d]Multivariate analysis of variance
[e]Electroencephalogram
[f]Analysis of covariance
[g]Central Nervous System
[h]Global Field Potential
[i]Chronic Obstructive Pulmonary Disease

Pure-Tone Thresholds

Conventional audiometric range

Fourteen of the 19 studies (74%) utilized conventional pure-tone thresholds as an outcome measure (Chang et al., 2016; Fabry et al., 2011; Gopal et al., 2009; Kumar et al., 2013; Lisowska et al., 2017; Negley et al., 2007; Ohgami et al., 2011; Oliveira & Lima, 2009; Paschoal & Azevedo, 2009; Prabhu et al., 2017; Ramikissoon & Cole, 2011; Sekher et al., 2017; Sumit et al., 2015). Inspection of Table 1 reveals that the studies were performed on current smokers, individuals who have either never smoked or not smoked in five or more years, as well as passive smokers, or those who do not actively smoke, but are exposed to smoke in some way. Table 5 shows the outcome measures, procedures, and findings of the the studies on effects of smoking on the conventional pure-tone thresholds.

As seen from inspection of Table 5, no statistically significant differences in conventional pure-tone thresholds between smokers and non-smokers were seen in in 3 of the 14 studies (21%) (Lisowska et al., 2017; Ohgami et al. 2011; Ramkissoon & Cole, 2011). Ramkissoon and Cole found no significant difference in conventional pure-tone thresholds between smokers and non-smokers when examining the presence or absence of mild (PTA > 25 dB dB HL), moderate (PTA > 40 dB dB HL), severe (PTA > 60 dB HL) hearing loss, or reduced word-recognition score (WRS < 88%). Ohgami et al. found no significant differences in mean thresholds (1 – 8k Hz) between smokers and non-smokers. Gopal et al. (2009) found that conventional pure-tone thresholds (3-frequency PTA at .5, 1, and 2k Hz) did not account for variance in CO levels of participants. Lisowska et al. found worse pure-tone thresholds in smokers than in non-smokers at all frequencies tested (.25 – 20k Hz), but these results failed to reach significance. Although no significant differences among groups occurred on the pure-tone thresholds, Ramkissoon and

Cole did find that both younger participants, when compared to older participants as well as smokers compared to non-smokers overestimated their self-reported hearing impairment.

Inspection of Table 5 also reveals that in the remaining 11 of the 14 (79%) studies, the pure-tone thresholds were significantly poorer in smokers than in non-smokers and passive smokers. Although the pure-tone thresholds were worse in smokers than in non-smokers and passive smokers, the thresholds did not always fall outside the normative hearing range (25 dB HL). In several studies, smokers had significantly poorer mean thresholds across the frequency range (.25 – 8k Hz) than non-smokers (Kumar et al., 2013; Negley et al, 2015; Oliveira & Lima, 2009; Prabhu et al., 2017). Kumar et al found that the severity of hearing loss (based on the 4-frequency PTA across .5, 1, 2, and 4k Hz) increased significantly as the duration of smoking and number of cigarettes smoked increase. Negley et al., who analyzed the thresholds at .25 to 8k Hz data using three-factor ANOVAs (subject group x ear side x hearing level), found that the mean hearing thresholds of smokers were significantly poorer than those for non-smokers, with maximal effects noted at 6 and 10k Hz. . Oliveira and Lima found significantly higher mean thresholds at .25 – 6k Hz in smokers (mean = 11.4 dB HL) compared with non-smokers (mean = 9.4 dB HL). Although Prabhu et al. primarily examined the pure-tone thresholds at the ultra high frequencies, significant differences were noted at 8k Hz with smokers having a poorer mean threshold than non-smokers. Although exact valus were not reported, based on inspection of the figures, the mean pure-tone threshold at 8k Hz was estimated to be 26 dB HL for smokers and 12 dB HL for non-smokers. Kumar et al., who examined the 4-frequency PTA (based on .5, 1, 2, and 4k Hz), found that the prevalence of hearing impairment was higher in smokers (66%) than non-smokers (15%). Sekher et al. (2017), reported on the prevalence of sensorineural hearing loss based on pure-tone thresholds, rather than on the degree of hearing loss, in smokers and non-

smokers. They observed significantly higher prevalence of sensorineural hearing loss in smokers (48%) than in non-smokers (22%).

Note from Table 5 that in terms of population-based studies, Chang et al. (2016) found statistically significant differences in the prevalence of hearing loss between smokers and non-smokers across age groups. They also noted significant differences in speech (5-frequency PTA) and high frequency PTA (3-frequency). Specifically, smoking prevalence was significantly related to speech frequency hearing loss (thresholds of ≥ 25 dB HL at .5, 1, 2, 3, 4k Hz) in participants aged 40 – 69 years, as well as to high frequency-hearing loss (present if thresholds ≥ 25 dB HL at 3, 4, and 6k Hz) in participants aged 30-79 years. Current smokers also had a higher prevalence of hearing loss overall compared to both passive and non-smokers in the 40 – 60 year age range. After adjusting to age, sex, and noise exposure, the mean speech-frequency PTA was significantly higher, by 2.5 dB HL (± .33 dB) in smokers than non-smokers; it was also significantly higher by 1.6 dB HL (± .33 dB) in smokers than passive smokers Additionally, passive smokers exhibited a higher prevalence of hearing impairment than non-smokers across all age groups, although this finding failed to reach significance in any age group. The passive smoking group exhibited significantly poorer mean speech frequency PTA (2.41 dB HL ± .47 dB) than non-smokers (1.2 dB HL ± .34 dB).

Table 5 further shows that Fabry et al. (2011) found a significant correlation between SHS exposure and the presence of low-mid frequency hearing loss (PTA > 25 dB HL based on .5, 1, and 2k Hz) and a significant correlation between former smoking behavior and the presence of high- frequency hearing loss exceeding 25 dB HL (4-frequency PTA based on 3, 4, 6, 8k Hz).

Table 5 shows that in one study, although a significant difference in pure-tone threshold occurred at just a single frequency (8000 Hz) in the left ear between smokers (mean of 4.5 dB HL) and non-smokers (mean of 3.3 dB HL), significantly more smokers than nonsmokers presented with tinnitus, and smokers with tinnitus had poorer pure-tone thresholds (.25 – 6k Hz) than smokers without tinnitus (Paschoal & Azevedo, 2009). Similarly, Rogha et al. (2015) found poorer mean thresholds at 2000 and 8000 Hz in smokers compared with non-smokers. Based on inspection of the figures, the estimated mean pure-tone threshold at 2000 Hz was 8 dB HL in smokers and 3 dB HL in non-smokers; at 8000 Hz, the estimated mean pure-tone threshold was 14 dB HL for smokers and 8 dB HL for non-smokers.

Table 5

Smoke-Exposure and Outcome Measure, Procedures, and Pure-Tone Threshold Results

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
Chang et al (2016)	12,935	Q[a]	Smoking status	Estimated prevalence of both speech frequency hearing impairment (present if thresholds of ≥25 dB HL at .5, 1, 2, 3, 4k Hz) and high frequency hearing impairment (present if thresholds ≥ 25 dB HL at 3, 4, and 6k Hz) according to smoking status and stratified by age group	PTT[b] testing done in soundproof booth inside mobile van using aura-aural headphones, automated testing.	Smoking related to speech frequency bilateral HL in age 40 - 69 - Current smoking group higher prevalance of HL than passive or non-smoking group in 40 - 60 age groups (OR[c] of 1.39 for smokers); high frequency HL in age 30 - 79 - current smoking group higher prevalance of HL than passive or non-smokers (OR of 1.42 for smokers); Current smokers had high PTA[d] thresholds than non-smokers and passive smokers***; passive smokers had higher PTA thresholds than non-smokers***
Fabry et al (2011)	5147	Q and serum cotinine levels	Smoking status	Prevalence of low-mid frequency HL (PTA > 25 dB HL at .5, 1, and 2k Hz) and high frequency HL (PTA at 3, 4, 6, 8k Hz > 25 dB HL)	Measured at .5, 1, 2, 3, 4, 6, 8k Hz (low-mid = .5, 1, 2k Hz; high = 3, 4, 6, 8k Hz)	Correlation between secondhand smoke exposure and low/mid frequency HL** and for high frequency HL for former smokers***
Gopal et al (2009)	16	Q and breath CO[e]	Breath CO levels	PTT (.25 - 8k Hz), pure tone average 500, 1000, and 2000 Hz; ART[f] measured ipsilaterally and contralaterally; ABR[g] latency and amplitude of wave V; TEOAE[h] measured at 1, 1.4, 2, 2.8,	PTT performed in sound treated room; AEP recorded to rarefaction clicks at intensity levels of 40 - 80 dB nHL	NS[i]

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
				and 4k Hz; DPOAE[j] measured at 1, 1.4, 2, 2.8, and 4k Hz; MLR[k] peak latency and amplitude of Na and Pa		
Kumar et al (2013)	148	Q	Smoking status	Presence of HL defined as PTA (.5 - 4k Hz) >25 dB in the worse ear. Severity classified as mild (>25 and ≤ 40 dB), moderate (>40 ≤ 60 dB) and severe (>60 dB)	PTT (.5k-6kHz)	Significantly higher PTT overall in smoking group*; severity significantly correlate with # cigarettes smoked and duration of smoking*
Lisowska et al (2017)	84	Q	Smoking status	PTT and HFA[l] mean thresholds at each frequency, presence or absence of CEOAE[m], SOAE[n], and DPOAE for non-smokers vs smokers, female smokers vs female non-smokers, male smokers vs male non-smokers, female non-smokers vs male non-smokers, female smokers vs. male smokers	PTT (.25k-8k Hz; HFA (8k-20kHz); sound treated room; CEOAE (present at response ≥ 3 dB SPL, reproducability > 75%), SOAE (similar to CEOAE - unreported), DPOAE (SNR > 3 dB)	Higher PTT in smokers - NS
Negley et al (2007)	24	Q	Smoking status	PTT - .25-8k Hz; HFA - 10-20k Hz; DPOAE - 2-8k Hz	PTT at 0.25-8kHz); HFA at 10-20kHz; DPOAE at 2-8kHz).	PTT .25 - 8k Hz poorer**

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
Ohgami et al (2011)	51	Q	Smoking status re BI	Average thresholds at 1 - 12k Hz of smoking and non-smoking group	PTT (1k-12kHz)	PTT poorer at 12k Hz in smokers*, no differences in auditory thresholds from 1 - 8kHz
Oliveira & Lima (2009)	60	Q	Smoking status	Mean thresholds in low frequency (.25 - 8k Hz) range and high frequency (9 - 18k Hz)	PTT .25, .5, 1, 2, 4, 6, 8k Hz; HFA 9, 10, 11.2, 12.5, 14, 16, 18k Hz	Significantly higher PTT overall (RE & LE) in smokers and non-smokers****,
Paschoal & Azevedo (2009)	144	Q	Smoking status	Occurrence of tinnitus, PTT at .25 - 8k Hz, HFA at 10000, 12500, 14000, and 16000 Hz, TEOAE response, and presence of TEOAE[o] suppression	PTT(.25-8kHz) and HFA (10-16kHz) measured in sound-proof booth	Worse thresholds for those with tinnitus, than those without***, worse PTT between .25 - 6K Hz in smokersNS, and 8000Hz left ear* (median of 5 in smokers and 2.5 in non-smokers)
Prabhu et al (2017)	50	Q	Smoking status	HFA thresholds at 8, 9, 10.225, 12.5, and 16k Hz. DPOAE amplitude at 8, 9, 10.25, 12.5, 14, and 16k Hz	HFA conducted using HAD-200 headphones. DPOAEs conducted in sound-treated room	Poorer PTT smokers**.
Ramkissoon & Cole (2011)	170	Subject report and urine test for prescence/absence of nicotine and cotinine	Smoking status	Presence or absence of mild (PTA > 25 dB), moderate (PTA > 40 dB), severe (PTA > 60 dB) and speech (WRS[p] < 88%) impairment	Self reported hearing impairment, PTT .25, .5, 1, 2, 4, 6, 8k Hz, speech reception threshold, word recognition	NS

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
Rogha et al. (2015)	32	Q	Smoking status	Mean thresholds at .25 - 16k Hz; Abnormal results for DPOAE/TEOAE considered <6 at 1 000, 2000, 4000, and 6000 Hz	Pure tone testing using AC 40 clinical audiometer; OAE performed using Eclipse EP25 device	Higher thresholds at 2000 and 8000 Hz in smokers compared to non-smokers ***
Sekher et al (2017)	120	Q	Smoking status	Presence or absence of mild, moderate, or severe SNHL[q]		Prevalence of SNHL higher in smokers
Sumit et al (2015)	184	Q	Smoking status	Presence of low/mid frequency HL if PTA of 1 and 4k Hz exceeded 20 dB, and high frequency HL if PTA at 8 and 12k Hz exceeded 40 dB	PTT (1k 4k, 8k, 12kHz) measured in soundproof booth using iPod with headphones	Smoking related to significantly worse PTT at 8 and 12k Hz*; PTT signficantly worse in those who smoked >5 years than those who smoked 1 - 5 years at 12k Hz***; Prevalence of HL was higher in smokers of both age groups*; Controlling for age and BMI, smoking increases liklihood of HL 4.9, 4.74, 5.04, and 2.85 times for 12, 8, 4, and 1k Hz, respectively***

[a]Questionnaire
[b]Pure Tone Threshold
[c]Odd's Ratio
[d]Pure Tone Average
[e]Carbon Monoxide
[f]Acoustic Reflex Threshold
[g]Auditory Brainstem Response
[h]Transient Evoked Otoacoustic Emissions
[i]Non-significant
[j]Distortion Product Otoacoustic Emissions
[k]Middle Latency Responses
[l] High Frequency Audiometry
[m]Click Evoked Otoacoustic Emissions
[n]Spontaneous Otoacoustic Emissions
[o]Transient Evoked Otoacoustics Emissions
[p]Word Recognition Score
[q]Sensorineural hearing loss

*p <0.05
**p <0.01
***p <0.00

Extended high-frequency pure-tone thresholds

Extended high-frequency pure-tone thresholds (i.e., at frequencies above 8000 Hz) were assessed as an outcome measure in 8 of the 19 studies, (42%) (Lisowska et al., 2017; Negley et al., 2007; Ohgami et al., 2011; Oliveira & Lima, 2009; Paschoal & Azevedo, 2009; Prabhu et al., 2017; Rogha et al., 2015; Sumit et al., 2015). Table 6 shows the outcome measures, procedures, and findings of the studies on effects of smoking on the extended high-frequency pure-tone thresholds. In 2 of these 8 studies (25%), however, the only extended high-frequencies examined were 10 – 12kHz, and these frequencies were included within the conventional audiometric frequency range (Ohgami et al.; Sumit et al). Although no significant differences between smokers and non-smokers were found in 2 studies (Negley et al.; Rogha et al.), significant differences in extended high-frequency thresholds between smokers and non-smokers were obtained in the remaining 4 (80%) of the studies assessing ultra high frequencies separate from the conventional pure tone range. In three of these studies, significantly worse thresholds at all frequencies (10 – 16k Hz) were obtained in smokers compared with non-smokers (Lisowska et al.; Oliveira & Lima; Prabhu et al.). Paschoal and Azevedo, on the other hand, found significantly worse high-frequency thresholds in smokers than in nonsmokers at only 12,000 and 14,000 Hz; at 12k Hz. They reported that the mean threshold was 31 dB HL in smokers versus 21 dB HL in non-smokers; at 14k Hz, the mean threshold was 38 dB HL in smokers versus 28 dB HL in non-smokers.

Inspection of Table 6 shows that Sumit et al. (2015), examining only 10 – 12k Hz in terms of extended high-frequency pure-tone thresholds, reported that current smokers with a history of smoking for more than 5 years had significantly worse pure-tone thresholds at 12k Hz

than current smokers with a history of smoking for only 1 – 5 years. This finding is suggestive of a dose effect, or an increase in hearing thresholds with increases in years of smoking. Ohgami et al. (2011) found poorer mean pure-tone thresholds at all frequencies across the frequency range from .25 to 12k Hz in smokers compared to non-smokers. Significant differences, however, in mean pure-tone threshold between smokers (estimated mean of 37 dB SPL, based on inspection of the figure) and non-smokers (estimated mean of 29 dB SPL, based on inspection of the figure) occurred only at 12k Hz.

Table 6

Smoke-Exposure and Outcome Measure, Procedures, and Ultra High-Frequency Pure-Tone Threshold Results

Study	N	Smokers Defined as	Measure of Smoke Exposure	Outcome Measures	Description of Outcome Measure	Procedure	Results
Lisowska et al (2017)	84	Q[a]	Smoking status	PTT[b], HFA[l], CEOAE[m], SOAE[n], DPOAE[j]	PTT and HFA mean thresholds at each frequency, presence or absence of COAE, SOAE, and DPOAE for non-smokers vs smokers, female smokers vs female non-smokers, male smokers vs male non-smokers, female non-smokers vs male non-smokers, female smokers vs. male smokers	PTT (.25k-8k Hz; HFA (8k-20kHz); sound treated room; CEOAE (present at response ≥ 3 dB SPL, reproducability > 75%), SOAE (similar to COAE - unreported), DPOAE (SNR > 3 dB)	Higher high frequency PTT in smokers[NS]
Negley et al (2007)	24	Q	Smoking status	PTT & HFA (subject group x ear side x hearing level as a function of test frequency), DPOAE (subject group x ear side x test frequency as a function of SNR[r] and absolute amplitudes)	PTT - .25-8k Hz; HFA - 10-20k Hz; DPOAE - 2-8k Hz	PTT at 0.25-8kHz); HFA at 10-20kHz; DPOAE at 2-8kHz).	NS[i]
Ohgami et al (2011)	51	Q	Smoking status re: BI[s]	PTT	Average thresholds at 1 - 12k Hz of smoking and non-smoking group	PTT (1k-12kHz)	PTT poorer at 12k Hz in smokers*, no differences in

Study	N	Smokers Defined as	Measure of Smoke Exposure	Outcome Measures	Description of Outcome Measure	Procedure	Results
							auditory thresholds from 1 - 8kHz
Oliveira & Lima (2009)	60	Q	Smoking status	PTT, HFA	Mean thresholds in low frequency (.25 - 8k Hz) range and high frequency (9 - 18k Hz)	PTT .25, .5, 1, 2, 4, 6, 8k Hz; HFA 9, 10, 11.2, 12.5, 14, 16, 18k Hz	Significantly higher PTT overall (RE & LE) in smokers and non-smokers****,
Paschoal & Azevedo (2009)	144	Q	Smoking status	PTT, HFA, TEOAE[o]	Occurrence of tinnitus, PTT at .25 - 8k Hz, HFA at 10000, 12500, 14000, and 16000 Hz, TEOAE response, and presence of TEOAE suppression	PTT(.25-8kHz) and HFA (10-16kHz) measured in sound-proof booth	Worse high frequency PTT at 12000 and 14000 Hz in smokers (median of 20 in non-smokers and 30 in smokers)***
Prabhu et al (2017)	50	Q	Smoking status	PTT, HFA, DPOAE	HFA thresholds at 8, 9, 10.225, 12.5, and 16k Hz. DPOAE amplitude at 8, 9, 10.25, 12.5, 14, and 16k Hz	HFA conducted using HAD-200 headphones. DPOAEs conducted in sound-treated room	Poorer HFA for smokers**. Positive correlation between HFPTT and number of years smoking*, number of cigarettes smoked per day*, and frequency of smoking*
Rogha et al. (2015)	32	Q	Smoking status	PTT, DPOAE, TEOAE, HFA	Mean thresholds at .25 - 16k Hz; Abnormal results for DPOAE/TEOAE considered <6 at 1 000, 2000, 4000, and 6000 Hz	Pure tone testing using AC 40 clinical audiometer; OAE performed using Eclipse EP25 device	NS

Study	N	Smokers Defined as	Measure of Smoke Exposure	Outcome Measures	Description of Outcome Measure	Procedure	Results
Sumit et al (2015)	184	Q	Smoking status	PTT	Presence of low/mid frequency HL if PTA of 1 and 4k Hz exceeded 20 dB, and high frequency HL if PTA at 8 and 12k Hz exceeded 40 dB	PTT (1k 4k, 8k, 12kHz) measured in soundproof booth using iPod with headphones	Smoking related to significantly worse PTT 12k Hz*; PTT signficantly worse in those who smoked >5 years than those who smoked 1 - 5 years at 12k Hz***; Controlling for age and BMI, smoking increases liklihood of HL 4.9, 4.74, 5.04, and 2.85 times for 12, 8, 4, and 1k Hz, respectively***

[a]Questionnaire
[b]Pure Tone Threshold
[c]Odd's Ratio
[d]Pure Tone Average
[e]Carbon Monoxide
[f]Acoustic Reflex Threshold
[g]Auditory Brainstem Response
[h]Transient Evoked Otoacoustic Emissions
[i]Non-significant
[j]Distortion Product Otoacoustic Emissions
[k]Middle Latency Responses
[l] High Frequency Audiometry
[m]Click Evoked Otoacoustic Emissions
[n]Spontaneous Otoacoustic Emissions
[o]Transient Evoked Otoacoustics Emissions
[p]Word Recognition Score
[q]Sensorineural hearing loss
[r]Signal to noise ratio
[s]Brinkman Index

*p <0.05
**p <0.01
***p <0.001

Otoacoustic Emissions

Six of the 19 (32%) studies utilized OAEs, such as transient evoked otoacoustic emissions (TEOAEs), distortion product otoacoustic emissions (DPOAEs), click-evoked otoacoustic emissions (CEOAEs), and spontaneous otoacoustic emissions (SOAEs), as an outcome measure (Gopal et al., 2009; Lisowska et al., 2017; Negley et al., 2007; Paschoal & Lima, 2009; Prabhu et al., 2017; Rogha et al., 2015). Table 7 shows the outcome measures, procedures, and findings of the the studies on effects of smoking on OAEs. As seen from Table 7, all studies employed a questionnaire as an indicator of smoke exposure. Only one study involved an objective indicator of smoke exposure; in that study the objective indicator was breath CO levels (Gopal et al.).

Inspection of Table 7 reveals that Prabhu et al. (2017) as well as Negley et al. (2007) obtained significantly lower mean DPOAE amplitude levels in smokers than in non-smokers at 8 – 16k Hz and at 2 – 8k Hz, respectively. Negley et al. observed this finding at both high (70 dB SPL) and moderate (65 and 50 dB SPL) intensities. Lisowska et al. (2017) also found significantly lower DPOAE amplitudes in smokers than in nonsmokers, but only at f2 = 1685 Hz in males. They also observed that the input/output function of DPOAE differed between male smokers and male non-smokers as well as male smokers and female smokers, but this result was not statistically significant. Gopal et al. (2009) found that DPOAE amplitude was a significant predictor of measured CO levels. Specifically, the DPOAE for the left ear decreased with increases in CO levels. Rogha et al. (2015) showed a decrease in DPOAE amplitude at 1000, 2000, 4000, and 6000 Hz in smokers compared with non-smokers, but found no significant differences in TEOAE amplitudes between groups.

Further review of Table 7 shows that not only did the overall occurrence of TEOAE responses as well as presence per frequency band at 3000 – 4000 Hz differ significantly between smokers and non-smokers, but also the incidence of absent TEOAEs was higher in-smokers then in non-smokers (Paschoal & Azevedo, 2009). Also, Lisowska et al. (2017) observed significantly lower levels of CEOAEs in male smokers compared with those in male non-smokers and in female smokers. But the difference in rates of present SOAEs between were male smokers and male non-smokers as well as between male and female smokers failed to reach significance.

Table 7

Smoke-Exposure and Outcome Measure, Procedures, and OAE Results

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
Gopal et al (2009)	16	Q[a] and breath CO[b]	Breath CO levels	PTT[c] (.25 - 8k Hz), pure tone average 500, 1000, and 2000 Hz; ART[d] measured ipsilaterally and contralaterally; ABR[e] latency and amplitude of wave V; TEOAE[f] measured at 1, 1.4, 2, 2.8, and 4k Hz; DPOAE[g] measured at 1, 1.4, 2, 2.8, and 4k Hz; MLR[h] peak latency and amplitude of Na and Pa	PTT performed in sound treated room; AEP[i] recorded to rarefaction clicks at intensity levels of 40 - 80 dB nHL	Right and left ear DPOAE**** variance accounted for in CO levels
Lisowska et al (2017)	84	Q	Smoking status	PTT and HFA[j] mean thresholds at each frequency, presence or absence of CEOAE[k], SOAE[l], and DPOAE[m] for non-smokers vs smokers, female smokers vs female non-smokers, male smokers vs male non-smokers, female non-smokers vs male non-smokers, female smokers vs. male smokers	PTT (.25k-8k Hz; HFA (8k-20kHz); sound treated room; CEOAE (present at response ≥ 3 dB SPL, reproducability > 75%), SOAE (similar to CEOAE - unreported), DPOAE (SNR > 3 dB)	Overall CEOAE levels lower in male smokers compared to male non-smokers and female smokers*, lower levels of DPOAE at f2=1685 Hz in male smokers*, I/O function of DPOAE differed between male smokers and male non-smokers/female smokers-NS[o], lower rates of SOAE in male smokers compared with male non-smokers/female smokers - NS
Negley et al (2007)	24	Q	Smoking status	PTT - .25-8k Hz; HFA - 10-20k Hz; DPOAE - 2-8k Hz	PTT at 0.25-8kHz); HFA at 10-20kHz;	Lower DPOAE amplitudes in smokers at high (70 dB SPL)* and

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
					DPOAE at 2-8kHz).	moderate (65 and 50 dB SPL)** intensity levels
Paschoal & Azevedo (2009)	144	Q	Smoking status	Occurrence of tinnitus, PTT at .25 - 8k Hz, HFA at 10000, 12500, 14000, and 16000 Hz, TEOAE response, and presence of TEOAE suppression	PTT(.25-8kHz) and HFA (10-16kHz) measured in sound-proof booth	Overall TEOAE responses as well as responses at 3000 - 4000 Hz in both ears sig. different in smokers**; higher incidence of absent TEOAE with normal hearing in smokers*; TEOAE suppression was also significantly different in both ears (medians of 3.2 smokers, 2.5 non-smokers)***
Prabhu et al (2017)	50	Q	Smoking status	HFA thresholds at 8, 9, 10.25, 12.5, and 16k Hz. DPOAE amplitude at 8, 9, 10.25, 12.5, 14, and 16k Hz	HFA conducted using HAD-200 headphones. DPOAEs conducted in sound-treated room	Reduction in DPOAE amplitude, including HFOAE[n]*
Rogha et al. (2015)	32	Q	Smoking status	Mean thresholds at .25 - 16k Hz; Abnormal results for DPOAE/TEOAE considered <6 at 1 000, 2000, 4000, and 6000 Hz	Pure tone testing using AC 40 clinical audiometer; OAE performed using Eclipse EP25 device	Decreased in DPOAE amplitude at 1000, 2000, 4000, and 6000 Hz in smokers compared to non-smokers ***

[a]Questionnaire
[b]Carbon Monoxide
[c]Pure Tone Threshold
[d]Acoustic Reflex Threshold
[e]Auditory Brainstem Response
[f]Transient Evoked Otoacoustic Emissions
[g]Distortion Product Otoacoustic Emissions
[h]Middle Latency Response
[i]Auditory Evoked Potentials
[j]High Frequency Audiometry
[k]Click Evoked Otoacoustic Emissions
[l] Spontaneous Otoacoustic Emissions
[m]Distortion Product Otoacoustic Emissions
[n]High Frequency Otoacoustic Emissions
[o]Non-significant
*p <0.05
**p <0.01
***p <0.001

Auditory Evoked Potentials

Smoking effects on AEPs were examined in 6 (32%) of the 19 studies. Table 8 shows the outcome measures, procedures, and findings of the the studies on effects of smoking on AEPs. As seen from inspection of Table 8, significant, adverse effects of smoking on the AEPs occurred in all included studies (Gopal et al., 2009; Guney et al., 2009; Gupta et al., 2008; Jawinski et al., 2016; Mosbacher et al., 2009; Ramkissoon & Chambers, 2008;). Gopal et al. (2009), who examined the auditory brainstem responses (ABR), found that the ABR peak wave V amplitude at 80 dB nHL in both ears accounted for variance in CO levels. The negative correlation between wave V amplitude and CO level was seen only in the left ear. For the left ear, Gupta et al. (2008) found significantly prolonged mean latencies for I, III, and V and significantly prolonged III-V and I-V interpeak latencies in smokers with COPD as compared with healthy non-smokers. Similar findings were obtained for the right ear, except that no significant difference between groups was obtained for the mean wave I peak latency; the mean peak latency for wave IV was significantly prolonged for wave IV in the group of smokers with COPD as compared with the control group; and the I-III interpeak latency also was significantly prolonged in the smokers with COPD as compared with the control group. In both ears, the peak amplitudes for waves I and V in the smokers with COPD were significantly reduced as compared with those for the control group. Additionally, in the left ear, the peak latency for waves I and III significantly correlated negatively with Forced Expiratory Volume (FEV) (r = -.37 and r = -.33, respectively) and the peak amplitude of wave I significantly correlated negatively with smoking packs years (r = -.34). In the right ear, the peak amplitude of wave I correlated positively with the duration of COPD illness (r = .38); the investigators did not speculate on a possible explanation of this finding. Of the COPD patients 65% presented with various ABR

abnormalities. Specifically, 60% presented with increased latencies of waves I – V and increased interpeak latencies of I – III, I – V, and III – V. A decrease in the amplitude of wave V – Va presented in 17.5% of patients and a decrease in wave I – Ia amplitude was noted in 12.5% of patients.

As seen in Table 4, Ramkissoon and Chambers (2008) compared auditory middle latency responses (MLRs) in non-smokers as well as smokers in the "chronic" condition and the "acute" condition. Inspection of Table 8 reveals that they employed an objective measure of smoking status. Additionally, they controlled for age by having age be a factor with two levels (older vs. younger adults) in the MANOVA. Initially, for the chronic condition, smokers were tested at the point in the day in which they had smoked half their total daily consumption of cigarettes but had abstained from smoking two hours prior to testing. Smokers were then tested again immediately after smoking a cigarette of their usual brand; this represented the acute condition. The results of MANOVA revealed the absence of a significant effect on Na-Pa amplitude when chronic smokers were compared with non-smokers; additionally, the interaction of age and smoking was nonsignificant. For the acute condition, the MANOVA results also revealed significantly larger Na-Pa amplitudes in the acute than in the chronic condition, in both age groups. The authors speculated that this finding possibly reflected an excitatory effect of nicotine that is similar to the excitatory effect of acetylcholine in the subcortical regions of the primary auditory pathway (inferior colliculus and thalamus to the cortex) and in the secondary auditory pathways (projections from the reticular formation to the thalamus and cortex). These regions serve as generator sites for Na and Pa.

As seen in Tables 4 and 8, Jawinkski et al. (2016) investigated N1-P2 amplitudes in those who had never smoked, ex-smokers, and current smokers. Significant differences were achieved

between ex-smokers and never smokers as well as current and never smokers, but not between ex- and current smokers. Individuals who had never smoked exhibited the highest N1-P2 amplitudes followed by ex-smokers and finally current smokers. The steepest increase of N1-P2 amplitudes across increasing presentation levels was found in those who had never smoked, followed by ex-smokers, and then by current smokers who demonstrated the shallowest increase. Packs per day and pack years was associated with reduced N1-P2 amplitudes at 72, 78, 84, and 90 dB SPL in ex- smokers.

Inspection of Table 8 further shows that two studies utilized the long-latency P300 to compare smokers with non-smokers (Guney et al., 2009; Mosbacher et al., 2009). Mobascher et al. found that those who never smoked had a higher P300 global field potential (GFP) than light smokers. Additionally, those who never smoked and light smokers had higher P300 GFPs than heavy smokers. The P300 current source density (CSD) was also reduced in smokers compared with those who never smoked, with heavy smokers having the lowest P300 CSD. In that study, the Fagerstrom test for nicotine dependence (FTND) was employed as the scale to represent an individual's physical dependence on nicotine (Heatherton et al., 199991). Following age, the FTND was the second best predictive of P300 GFP. Guney et al. reported that at Fz, the P300 and N1 amplitudes were reduced, and N1 latency was prolonged in smokers as compared with non-smokers. At Cz, N1 amplitude was also lower in smokers than in non-smokers.

Table 8

Smoke-Exposure and Outcome Measure, Procedures, and AEP Results

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
Gopal et al (2009)	16	Q[a] and breath CO[b]	Breath CO levels	PTT[c] (.25 - 8k Hz), pure tone average 500, 1000, and 2000 Hz; ART[d] measured ipsilaterally and contralaterally; ABR[e] latency and amplitude of wave V; TEOAE[f] measured at 1, 1.4, 2, 2.8, and 4k Hz; DPOAE[g] measured at 1, 1.4, 2, 2.8, and 4k Hz; MLR[h] peak latency and amplitude of Na and Pa	PTT performed in sound treated room; AEP[i] recorded to rarefaction clicks at intensity levels of 40 - 80 dB nHL	Right**** and left ear ABR peak V amplitude at 80 dBnHL**, right ear ABR peak V amplitude at 40 dBnHL**** were significant predictors of CO levels; these 5 predictors accounted for 75% of the variance in CO levels
Guney et al (2009)	64	Q	Smoking status	N1 latency and amplitude, P2 latency and amplitude, P300 latency and amplitude	ERP[j] recordings in quiet room; oddball paradigm -2kHz target tone presented 20% of the time, 1kHz non-target presented 80% of the time at 80 dB. Peak latencies measured at Cz and Fz	P300 amplitude at Fz was lower in smokers than non-smokers***; N1 amplitude at Fz was lower in smokers than in non-smokers**; N1 amplitude at Cz was lower in smokers than nonsmokers*; N1 latency at Fz was prolonged in smokers compared to nonsmokers*

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
Gupta et al (2008)	80	Q and GOLD[k] guidelines	Presence or absence of COPD[l], spirometry	Latencies of wave I, II, III, IV, and V, interpeak latencies of I-III, I-V, and III-V, amplitude of waves I and V	AEP recordings performed in sound-proof room with a click stimulus of 70 dB nHL at rate of 11.1/s	In both ears, COPD patients, prolonged wave I***; interpeak latencies of III-V and I-V prolonged in COPD patients vs. controls**; Amplitude of wave I and V were reduced in COPD patients***; LE: latencies of waves I, III, and V prolonged in COPD patients vs. controls***; latencies of waves II and IV also prolonged but were NS; wave III*** correlated negatively with FEV[m]; Amplitude of wave I correlated negatively with packs per years smoking* RE: latencies of waves III, IV, and V prolonged in COPD patients vs. controls***; interpeak latency of I-III were prolonged in the COPD group***; Amplitude of wave I correlated negatively with duration of illness**
Jawinski et al (2016)	1739	Q	Smoking status	N1 - P2 amplitude at 72, 78, 84, 90, and 96 dB SPL as well as mean intensities, the linear slope, and the median slope	N1-P2 amplitude at various intensities (linear and median slopes across intensities) in sound attenuated booth with insert earphones 450 pseudo-randomized 1k Hz tones (30 ms duration, 10 ms rise/fall times) at 5 calibrated intensities (72, 78, 84, 90, 96 dB SPL)	Never smokers exhibited highest N1-P2 amplitudes followed by ex-smokers and current smokers**; Significant difference between ex- and never smokers*, current and never smokers*, but not between ex- and current smokers; Steepest increase of N1-P2 amplitudes of

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
						never smokers, ex- with intermediate phenotype, and current smokers showing shallowest increase*; Never smokers steeper increase in N1-P2 amplitudes than ex-**; Packs per day and pack years associated with reduced N1-P2 amplitudes at 72,78,84, and 90 dB SPL in ex- smokers*; NS[p] dose effect for current smokers
Mobascher et al (2009)	1318	Q, COHb[n] measurement, FTND[o]	Age, smoking status, and gender	P300 amplitude	P300: oddball paradigm, 2kHz tone (target tone) presented 20% of the time, 1.5kHz tone (non-target tone) presented 80% of the time. Right-hand button press to target tone	NS effect of smoking status on P300 latency or reaction time.; Never smokers had higher P300 GFP[q] than light smokers**; Never smokers and light smokers had higher P300 GFP than heavy smokers***; P300 CSD[r] reduced in smokers compared to never smokers with heavy smokers having the lowest P300/P3b CSD; FTND was the second most predictive regressor of P300 GFP*** following age***

Study	N	Smokers Defined as	Measure of Smoke Exposure	Description of Outcome Measure	Procedure	Results
Ramkisson & Chambers (2008)	40	Q and urine analysis	Age and smoking status	Absolute latency of waves V, Pa, and Na, and relative amplitude of waves V-Na and Na-Pa on MLR	Rarefaction click stimuli presented at 70 dBnHL. Testing was performed on smokers after they had smoked half of their daily cigarette consumption, but were asked to abstain two hours prior to testing representing the chronic condition, smokers were tested again immediately after smoking a cigarette of their usual brand, representing the acute condition	When comparing non-smokers and chronic smokers , age accounted for 29% of the overall variance*; Na-PA amplitude was larger in acute compared to chronic smoking condition ***; Wave V latency was longer in older smokers compared to younger smokers*; NS for smoking behavior or interaction of smoking behavior and age

[a]Questionnaire
[b]Carbon Monoxide
[c]Pure Tone Threshold
[d]Acoustic Reflex Threshold
[e]Auditory Brainstem Response
[f]Transient Evoked Otoacoustic Emissions
[g]Distortion Product Otoacoustic Emissions
[h]Middle Latency Response
[i]Auditory Evoked Potentials
[j]Event Related Potentials
[k]Global Initiative for Chronic Obstructive Lung Disease
[l]Chronic Obstructive Pulmonary Disease
[m]Forced Expiratory Volume
[n]Carboxyhemoglobin
[o]Fagerstrom Test for Nicotine Dependence
[p]Non-significant
[q]Global Field Potential
[r]Current Source Density
*p <0.05
**p <0.01
***p <0.001

DISCUSSION

The purpose of this systematic review was to determine the effects of smoking on auditory function. Thus, studies examining a variety of outcome measures were included in the present systematic review. Significant findings were present across all outcome measures, including pure-tone thresholds, ultra high-frequency thresholds, OAEs, and AEPs, with the majority of studies controlling for age and other confounding factors including noise exposure and history of middle ear disorders.

Significantly worse thresholds were obtained in smokers compared to non-smokers in both ears and across the conventional audiometric frequency range (.25 – 8k Hz) in the majority of studies regardless of participant age (Chang et al., 2016; Fabry et al., 2011; Kumar et al., 2013; Negley et al., 2007; Oliveira & Lima, 2009; Prabhu et al., 2017; Sekher et al., 2017). Of note, a correlation was noted for those only exposed to secondhand smoke in the low – mid frequency range (.5 – 2k Hz) (Fabry et al.). Significant differences in pure-tone thresholds were also noted between those who never smoked and past smokers suggesting that the effects of cigarette smoke on the auditory system are long-lasting, regardless of smoking cessation (Chang et al.). Some discrepant findings were seen, however, as 3 studies did not obtain significant findings in this frequency region (Gopal et al., 2009; Ohgami et al., 2011; Ramkissoon & Cole, 2011). Past smokers who had quit at least 3 years prior to testing were included in the non-smoking group of one study in which results were non-significant (Ramkissoon & Cole). Perhaps the long-lasting effects of smoking previously mentioned contaminated these findings resulting in no significant differences between smokers and "non-smokers." Gopal et al. only included those with no history of hearing loss and examined a small sample size (16). Both of which may contribute to their non-significant findings. Ohgami et al. also did not achieve a significant result

in the conventional audiometric range, however, they did not examine the two lowest frequencies (.25 - .5 Hz) typically included in this range.

The aforementioned effects of smoking generally observed on the conventional pure-tone thresholds persisted in the ultra-high frequency range with both significantly worse thresholds in smokers compared to non-smokers and a dose effect of decreasing thresholds with an increase in smoke exposure (Ohgami et al., 2011; Oliveira & Lima, 2009; Paschoal & Azevedo, 2009; Prabhu et al., 2017; Sumit et al., 2015). Effects in this frequency range, however, were more frequency specific with the majority of significant findings obtained at 12 – 14k Hz (Ohgami et al., 2011; Oliveira & Lima, 2009; Paschoal & Azevedo, 2009; Sumir et al., 2015). Two studies noted these effects across the ultra-high frequency range (9 – 16k Hz, and 9 – 20k Hz) (Lisowska et al., 2017; Prabhu et al.); in one of these two studies however, the findings trended towards significance but failed to reach significance. Two studies did not find significant differences in this range between smokers and non-smokers, however, they each had a small sample size (Negley et al., 2007; Rogha et al., 2015).

Several subsets of OAEs were also measured and the results corroborate those noted for both the conventional pure-tone thresholds and ultra high-frequency thresholds. Decreases in the DPOAE and TEOAE amplitudes in the conventional frequency range were observed in smokers in several studies (Gopal et al., 2009; Lisowska et al., 2017; Negley et al., 2007; Paschoal & Azevedo, 2009; Prabhu et al., 2017; Rogha et al., 2015). In one study on DPOAEs in the ultra high-frequency range (9 – 16k Hz), amplitudes were significantly lower in smokers than non-smokers (Prabhu et al., 2017).

Significant effects of smoking were also found in AEP studies. Significant differences occurred across latencies for ABR, auditory MLR, and long latencies potentials including P300

(Gopal et al., 2009; Guney et al., 2009; Gupta et al., 2008; Jawinski et al., 2016; Mobascher et al., 2009; Ramkissoon & Chambers, 2008). Both studies examining ABRs obtained significant findings, however, one of which only noted a correlation between CO levels and wave V (Gopal et al.). Gupta et al., on the other hand, found significant differences in several measures including absolute latencies, interwave latencies, and amplitudes, but these effects were noted in individuals with COPD, thus representing those most severely affected by smoke exposure. Additionally, several findings in this study were ear-specific (Gupta et al.). While many studies examining MLRs and smoking have been conducted, only one isolated the effects of cigarette smoke and excluded those with psychological disgnoses. Significant findings, however, were achieved (Ramkissoon & Chambers). In contrast to the negative correlations found, Ramkissoon and Chambers observed a significantly larger Na-Pa amplitude in the acute than in the chronic smoking condition. Those investigators speculated this finding illustrates the arousal effects of nicotine that may be attributed to increase neural synchronization which presents as an excitatory response, or in this study, larger Na-Pa responses.

In the remaining AEP studies, significant smoking effects were obtained on the long latency potentials, specifically, N1-P2 and P300 (Guney et al., 2009; Jawinski et al., 2016; Mobascher et al., 2009). Significantly lower N1-P2 amplitudes were noted in smokers compared to non-smokers in the two studies which examined this measure (Guney et al.; Jawinski et al.). One of these studies also noted significantly prolonged N1 latency in smokers when compared to non-smokers. Similarly to N1-P2, of the two studies examining P300, both achieved significant results. Specifically reduced P300 responses were noted in smokers compared to those who had never smoked, and in one study, those categorized as light smokers (Mobascher et al.; Guney et al.).

A dose effect, illustrated in several different ways, was noted across outcome measures. In regards to pure tone thresholds, the effect was noted in smokers in several studies with thresholds increasing as smoke exposure, quantified as years smoking as well as packs per day, increased (Kumar et al.; Prabhu et al.; Sumit et al., 2015). Similar to that of pure tone thresholds, in one study, the amplitude of wave I in the right ear correlated negatively with duration of illness, and the right ear, and amplitude of wave I in the left ear correlating negatively with packs per years smoking (Gupta et al., 2008).

Supporting the idea of a dose effect, studies which examined either past smokers or those exposed to SHS found significant differences between the aforementioned groups and those with no smoke exposure at all, as well as significant differences between those groups and current smokers. Significant differences in pure-tone thresholds were also noted between those who never smoked and past smokers suggesting that the effects of cigarette smoke on the auditory system are long-lasting, regardless of smoking cessation (Chang et al.). This effect was also noted in studies examined AEPs as an outcome measure. Jawinski et al. found significantly higher N1-P2 amplitudes in persons who never smoked followed by ex-smokers with the next highest amplitude, and current smokers with the lowest N1-P2 amplitude. Although significant differences between never smokers and current smokers, as well as never smokers and ex-smokers were noted, no significant difference was noted between ex-smokers and current smokers. Participants, however, in the ex-smoking group had quit smoking a minimum of 12 months prior to this study. Perhaps if ex-smokers had quit far longer prior to this study, significant differences would have been achieved between these two groups. As mentioned previously, despite smoking cessation, perhaps long term effects of smoking persist, thus rendering differences in N1-P2 amplitude between ex- and current smokers non-significant.

Supporting such, a significant dose effect was seen (N1-P2 amplitude inversely related to packs per day and pack years) in ex- smokers (Jawinski et al., 2016). Effects were noted in P300 amplitude as well with persons who never smoked having significantly higher P300 GFP than light smokers and similarly, persons who never smoked and light smokers had higher P300 GFP than heavy smokers (Mobascher et al., 2009).

While a comparison can only be made in terms of conventional pure tone thresholds, as the past review only included such, the present systematic review corroborates the aforementioned meta-analysis, with positive correlations found in the majority of included studies (Nomura, Nakao, and Morimoto, 2005). Furthermore, caution should be taken when comparing the two reviews for several reasons. Nomura, Nakao, and Morimoto did not include studies involving passive smokers and included those exposed to noise, in contrast to the present review. Additionally, a vast majority of studies in the Nomura, Nakao and Morimoto review did not adjust for age related differences. It should also be noted that subjects in studies published after the meta-analysis, and those included in this review, were excluded if they had a history of noise exposure whereas subjects with noise exposure histories were included in the studies evaluated by Nomura, Nakao, and Morimoto. Statistical analyses, however, were performed to adjust for noise exposure (Nomura, Nakao, & Morimoto).

The majority of studies (17 of 19) controlled for age in some capacity, whether it be only including younger participants, delineating “younger” and “older” groups, statistically adjusting for age, or age-matching control groups. Many, (15 of 19) however, did not adjust for gender nor compare the results of male and female smokers and non-smokers. One study examining OAEs, conventional pure tone thresholds, and ultra high frequency thresholds, found significant differences between genders, with more significant effects occurring in male particpants, thus

justifying the need for future research considering such (Lisowska et al., 2017). Very few studies (3 of 19) included passive smokers and/or ex-smokers. As a dose effect was noted in several studies across outcome measures when comparing passive smokers, ex-smokers, current smokers, and non-smokers, future research delineating such groups is needed. Only 6 studies utilized any form of auditory evoked potential, with 2 examining ABRs, 1 examining MLR and the remaining 3 examining long latency potentials such as N1-P2 and/or P300. While significant differences between smokers and non-smokers were achieved, future research is needed to corroborate these findings. Additionally, one study examining ABRs obtained ear specific significant differences between smokers and non-smokers (Gupta et al., 2008). Thus, future research is needed to repeat the study with a larger sample size to see if these findings would occur in both ears.

CONCLUSION

The adverse effects of cigarette smoke on auditory function are present and clear throughout the literature reviewed. As a result, smoking behavior should be avoided due to its effects on auditory function, as well as the myriad of other heavily researched deleterious side effects. Specific to the effects on auditory function, it would be advantageous to include a question of smoking behavior in an audiologic evaluation intake form. This question should also probe systematic exposure to secondhand smoke due to the effects of passive smoking. Additionally, smoking cessation can be recommended to reduce effects on auditory function.

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