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A systematic review of the impact of cigarettes and electronic cigarettes in otology

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Abstract

Background. The detrimental systemic effects of cigarette smoking are well established. Though less pronounced in the field of otology, they are proposed to contribute to the global burden of unaddressed hearing loss. Recently, in efforts to stop smoking, individuals have used electronic cigarettes of which the long-term safety data are largely unknown. This study aimed to conduct a systematic review of cigarette smoking and electronic cigarette effects in the field of otology.
Method. Relevant articles were identified by a National Institute for Health and Care Excellence healthcare database literature search and by scanning the references of relevant articles and reviews.
Results. A total of 473 articles were identified, with 43 articles included in the review after trials were excluded.
Conclusion. Cigarette smoking is associated with recurrent otitis media, otitis media with effusion and sensorineural hearing loss in children exposed to second-hand smoke. In adults, it is associated with active and aggressive chronic suppurative otitis media, worse tympanoplasty success rates, increased post-operative complications and sensorineural hearing loss that is more pronounced in the long term and at high frequencies. The effects of e-cigarettes in otology are largely unknown.

Review Article

Dr S Patel takes responsibility for the integrity of the content of the paper

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Introduction

The association between cigarette smoking and lung cancer was first demonstrated in the pioneering epidemiological study of smoking doctors by Doll and Hill in 1954.[1] Further research and epidemiological data have highlighted the deleterious role of cigarette smoking particularly in head and neck cancer, coronary artery disease and respiratory disease. Such is the global impact of cigarette smoking that the World Health Organization (WHO) considers it to be the most avoidable cause of illness and death worldwide.[2] Within the field of otology, the effects of cigarette smoking are less pronounced but have been associated with both middle- and inner-ear pathology. This association has been seen most publicly through otitis media in children exposed to second-hand smoke but also with adverse outcomes following otological surgery and sensorineural hearing loss (SNHL). Fortunately, cigarette smoking is declining owing to public health initiatives.[3]

Electronic cigarettes, also known as electronic nicotine delivery systems or vapes, have grown in popularity over the past decade.[4] These devices consist of a battery, a vaporising chamber and an electronic liquid. The electronic liquid solution consists of propylene glycol, ethylene glycol, a flavoured solution and nicotine. Users can gradually select electronic liquids containing reducing doses of nicotine in the effort to stop smoking. Currently, it is unknown whether electronic cigarettes are as effective as other nicotine replacement therapies, but their popularity has risen because of their similar method of administration to cigarettes and the variety of flavours available.[5] Despite this, there has been growing concern that these devices could act as a gateway to nicotine addiction and cigarette smoking particularly amongst children and adolescents.[6] Within otology, the effects on middle-ear and inner-ear pathology are largely unknown but *in vitro* studies and historical animal studies may provide insight into possible effects.

The WHO estimates that 466 million individuals suffer from disabling hearing loss with a predicted global economic burden of 750 billion US dollars.[7] In adults, it can lead to social isolation and in children can disrupt speech and language development, restricting academic and social progress. As such, it is imperative that modifiable risk factors for hearing loss are identified and targeted. This systematic review aims to provide an up-to-date overview of the latest data on cigarette smoking and its effects on middle-ear disease, hearing loss and surgical outcomes, including the latest evidence on electronic cigarettes in otology.

Materials and methods

A National Institute for Health and Care Excellence (NICE) healthcare database advanced literature search was conducted using the search terms shown in Table 1. No restrictions were made during the search, and a total of 473 articles were identified. Further literature

Table 1. Search terms used to identify relevant literature

Search terms
Hearing loss
Hearing impairment
Deafness
Ear disease
Otitis media
Otitis media with effusion
Chronic otitis media
Suppurative otitis media
Cholesteatoma
Ear surgery
Middle ear surgery
Ossiculoplasty
Tympanoplasty
Myringoplasty
Mastoidectomy
Tobacco smoking
Cigarette smoking
Parental smoking
Electronic cigarette
Vape
Electronic nicotine delivery system
Nicotine
Propylene glycol
Ethylene glycol

was identified by scanning the references of relevant articles and reviews. The inclusion criteria were: studies that investigated the impact of cigarettes on middle-ear disease, otological surgery and SNHL. For the impact of electronic cigarettes, studies on any aspect of ear disease or otological surgery were included. The reasons for exclusion were: irrelevance, non-English language and availability to the authors. Where studies were already included in a meta-analysis, combined data were presented from the meta-analysis rather than as data from individual trials to report effect estimates of increased precision, validity and of greater power. A total of 42 studies were included in this systematic review.

Cigarettes and middle-ear disease and surgery

Exposure to cigarette smoking may affect the middle-ear function via a number of mechanisms. Cigarette smoke is proposed to impair the beating function of cilia and cause hypersecretion of mucous by goblet cells within the Eustachian tube. This leads to Eustachian tube obstruction, dysfunction and trapping of mucus and bacteria within the middle ear with subsequent otitis media. Mast cell degradation, adenoidal tissue hyperplasia and impaired phagocytic function are further proposed to contribute to Eustachian tube dysfunction.[8]

Pooled data from 7 homogeneous studies demonstrated that children exposed to second-hand smoke had a 48 per cent increased odds of developing recurrent acute otitis media (95 per cent confidence interval (CI), 1.08–2.04) and pooled data from 4 homogeneous studies demonstrated exposed children had a 38 per cent increased odds of developing otitis media with effusion (OME) (95 per cent CI, 1.23–1.55) compared with non-exposed children.[9]

A further large, industry funded systematic review of 58 trials by Thornton and Lee suggested the association between second-hand smoke exposure and recurrent acute otitis media (11 trials) and recurrent OME (23 trials) was present but weak owing to overestimation of the effect due to inconsistent adjustment for confounders and selection and information bias. Unfortunately, no meta-analyses of the data or calculation of heterogeneity was performed.[10]

In the most recent meta-analysis, pooled data from 14 studies demonstrated that children exposed to second-hand smoke because of post-natal maternal smoking had a 53 per cent increased odds of all cause middle-ear disease (acute otitis media, OME, recurrent otitis media and chronic otitis media) (95 per cent CI, 1.22–1.92). Furthermore, pooled data from 38 studies demonstrated children exposed to household second-hand smoke had 32 per cent increased odds of developing all cause middle-ear disease. However, considerable heterogeneity was seen in both analyses ($I^2 = 73$ per cent and $I^2 = 73$ per cent, respectively) owing largely to a variety of different observational study designs, methodological quality of studies and incomplete adjustment of confounders.[11] Smoking cessation has been advocated as a key measure to address acute otitis media in low income environments, and NICE recommends parents of children with OME are advised that second-hand smoke exposure increases the risk of recurrent OME.[12,13]

Cigarette smoking is associated with an increased risk of developing chronic suppurative otitis media (CSOM). In one trial from India ($n = 4143$), smokers had a 13 per cent increased odds of developing CSOM than non-smokers, and in another study, 68 per cent of patients with ear canal cholesteatoma were found in current or former smokers.[14,15] In addition, smokers with CSOM have been found to have higher rates of active disease demonstrated by increased rates of otorrhoea and higher rates of aggressive cholesteatoma disease demonstrated in one study by a higher rate of further complications including exposed dura, exposed facial nerve and labyrinthine fistula.[16] This may be attributable to antigenic substances within cigarette smoke that are proposed to induce an inflammatory response in middle-ear mucosa transforming it into a more secretory type.[8]

Prognostic effects of cigarette smoking on middle-ear surgery have been investigated in several trials and have been subject to a prior review assessing outcomes up to six months (Table 2).[8,16–25] Cigarette smoking is proposed to lead to poorer outcomes because of defective middle-ear aeration secondary to the effects described above and also because of the vasoconstrictive effects of nicotine which have been demonstrated to adversely affect neovascularisation of newly grafted tissue.[26]

Trials have reported graft uptake results ranging from 40 to 100 per cent following tympanoplasty (Table 2). Trialists with increased success rates amongst smokers have attributed this to use of cartilage grafts rather than temporalis fascia owing to its metabolic properties and resistance to retraction, atelectasis and perforation.[21,24,25] In one trial utilising both graft tissues, a 75 per cent failure was reported amongst smokers when temporalis fascia was used compared with similar success rates between smokers and non-smokers (88.9 per cent and 76.8 per cent, respectively) when cartilage grafts were used, further advocating the use of cartilage as routine in smokers.[19]

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Table 2. Graft uptake and audiological outcomes between smokers and non-smokers following tympanoplasty

Author	Participants (*n*)	Year	Graft material	Graft uptake in smokers (%)	Graft uptake non-smokers (%)	Was the post-operative difference in the air–bone gap between smokers and non-smokers significant?
Becvarovski and Kartush[8]	74	2001	Temporalis fascia	100 (at 6 months) 40 (long term)	100 (at 6 months) 79.8 (long term)	No
Onal *et al.*[18]	80	2005	Temporalis fascia	62	93	No
Uguz *et al.*[19]	77	2008	Temporalis fascia and cartilage	68	93	No
Kaylie *et al.*[16]	1183	2009	Not reported	Not reported	Significantly higher	Yes, but clinically small (3 dB)
Lin *et al.*[20]	62	2011	Cartilage	71	81	No
Coelho & Peng[21]	118	2012	Cartilage	89	95	No
Migirov *et al.*[22]	65	2013	Temporalis fascia and tragal perichondrium	100	96	No
Kyrodimos *et al.*[25]	52	2014	Cartilage	100	100	No
Naderpour *et al.*[23]	60	2016	Temporalis fascia	88.8	95.2	No
Cox *et al.*[24]	247	2016	Cartilage	99.4	98.7	No

Only one trial using temporalis fascia grafts reported similar outcomes between smokers and non-smokers and attributed this to the experience of the otologist, highlighting that alternative pre- and intra-operative factors may have a more profound effect on graft uptake rates.[22] Only one trial reported significantly increased odds of graft uptake failure in smokers despite using cartilage grafts (odds ratio, 8.16; 95 per cent CI, 1.74–36.89), but in this trial, an inlay technique was employed in contrast to the conventional underlay approach.[20] Trialists have reported largely similar audiological outcomes between smokers and non-smokers following tympanoplasty with and without ossicular chain reconstruction (Table 2).[17]

Smokers have been demonstrated to be at greater risk of post-operative complications. Becvarovski and Kartush found delayed perforation and atelectasis of the grafted tympanic membrane in 60 per cent of smokers ($n = 9$) compared with 20 per cent of non-smokers ($n = 12$) after 6 months following tympanoplasty.[8] In a separate study, 12 per cent of smokers ($n = 9$) developed post-operative OME or tympanic membrane atelectasis warranting further secondary tympanostomy tube placement compared with 1.2 per cent of non-smokers ($n = 2$). Furthermore, this trial also found a higher rate of recurrence of cholesteatoma disease in smokers ($n = 4$ (5.3 per cent)) compared with non-smokers ($n = 1$ (0.6 per cent)), although this was not demonstrated in studies by Kaylie *et al.* and Becvarovski and Kartush.[8,16,24] Coelho and Peng found a greater proportion of smokers required revision surgery for persistent cholesteatoma, conductive hearing loss and tympanic membrane perforation compared with non-smokers ($n = 6$ (13.3 per cent) and $n = 4$ (4.7 per cent), respectively).[21] In an assessment of 30-day post-operative outcomes following otological surgery, smokers have also been found to have increased odds of soft tissue complications including 89 per cent increased odds of superficial wound infections (95 per cent CI, 1.32–2.86) and almost 300 per cent increased odds of wound dehiscence (95 per cent CI, 1.26–11.60).[27]

Cigarettes and SNHL loss

Cigarette smoking is proposed to induce hearing impairment by inducing atherosclerosis within the internal auditory artery resulting in cochlear ischaemia and also through the direct ototoxicity of nicotine. The effect was demonstrated in early experimental studies in animals.[28] Similar trials in humans would be unethical; therefore, trialists have taken to observational study designs usually investigating the effect in conjunction with other atherogenic diseases. Pooled data in a meta-analysis of two homogeneous prospective cohort trials by Nomura *et al.* demonstrated cigarette smokers had almost double the risk (risk ratio, 1.97; 95 per cent CI, 1.44–2.70) of developing hearing loss compared with non-smokers.[29]

Newer prospective trials and trials excluded from the pooled analysis have, however, demonstrated inconsistent results. Over a 5-year period ($n = 705$) Karlsmose *et al.* demonstrated almost equivalent risk of hearing impairment between smokers and non-smokers (relative risk, 0.97; 95 per cent CI, 0.74–1.26), but in the longest prospective trial to date, Cruickshanks *et al.* demonstrated that current smokers were 36 per cent more likely to develop hearing loss greater than 25 dB than non-smokers over a 15-year period (95 per cent CI, 1.05–1.77), possibly suggesting that longer follow-up periods are required to demonstrate the association between smoking and hearing as oxidative stresses and atherosclerosis within the internal artery progress and cochlear ischaemia ensues.[30,31] Despite this, Nakanishi *et al.* demonstrated a significantly increased risk (relative risk, 2.45 CI, 1.28–4.70) of high frequency hearing loss greater than 30 dB amongst smokers as early as 5 years. This was only seen at 4 kHz in men indicating that the basal turn of the cochlea may be affected first in smoking-related hearing loss and therefore identified earlier when reported independent of other frequencies.[32] Certainly, trials investigating the character of early smoking-related hearing loss have found this to be more pronounced at higher frequencies.[33–35]

The impact of cigarette smoke on SNHL has been investigated extensively through cross-sectional or 'snapshot' studies. The results have also been inconsistent but pointed towards increased prevalence of hearing impairment amongst smokers. Pooled data from 5 cross-sectional trials demonstrated cigarette smokers had a 30 per cent increased risk of having hearing loss compared to non-smokers (95 per cent CI 1.24–1.44).

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However, considerable heterogeneity was found between trials due to the variance in the definition of hearing loss.[29]

More recently, a South Korean study ($n = 12\ 935$) demonstrated increased odds of bilateral high frequency hearing loss greater or equal to 25 dB (odds ratio 1.42; 95 per cent CI, 1.13–1.77) and bilateral hearing loss at speech frequencies (odds ratio 1.39; 95 per cent CI, 1.08–1.79) amongst smokers compared with non-smokers, indicating that cigarette smoking may be correlated not only with hearing loss but more importantly with clinically relevant hearing loss.[36] This is consistent with subjective data from prospective questionnaire-based studies that have demonstrated increased perceived hearing loss in smokers over a 5- and 10-year period compared with non-smokers.[37,38]

In a recent large UK cross-sectional trial ($n = 164\ 770$) utilising the speech-in-noise test rather than pure tone audiometry, Dawes *et al.* demonstrated that current smokers had a 15 per cent increased odds of developing hearing loss compared with non-smokers (95 per cent CI, 1.09–1.21).[39] In this study, a dose-related response was also demonstrated whereby long-term smokers had 30 per cent increased odds of hearing loss (95 per cent CI, 1.19–1.41) and medium-term smokers had 11 per cent increased odds of hearing loss (95 per cent CI, 1.03–1.19) compared with non-smokers. This was consistent with findings in the prospective trial by Nakanishi *et al.* where the risk of hearing loss significantly increased with increasing pack years.[32] Studies have demonstrated that former smokers have a reduced risk of hearing loss compared with current smokers, highlighting the importance of smoking cessation for hearing preservation.[29]

Exposure to second-hand smoke has been demonstrated to be harmful to cochlear physiology in children and adolescents exposed to second-hand smoke. This may occur as early as *in utero* as adolescents whose mothers smoked during pregnancy were demonstrated to have a 2.6-fold increased odds of unilateral low frequency hearing loss (95 per cent CI, 1.1–6.4) compared with children of non-smoking mothers.[40] Children 'heavily' exposed to cigarette smoke were found to have 3 times the risk of having hearing loss to 20–25 dB (95 per cent CI, 18–8.3), and in a another study, adolescents exposed to second-hand smoke had an 82 per cent increased odds of hearing loss above 15 dB (95 per cent CI, 1.08–3.41) compared with those non-exposed. In this latter study, those with the highest exposure, measured objectively through serum cotinine levels, demonstrated increased odds of hearing loss (odds ratio, 2.72; 95 per cent CI, 1.46–5.06) further supporting the notion of a dose-related response relationship.[41,42]

There is also a suggestion that cigarette smoking has a synergistic effect on age-related hearing loss and noise-induced hearing loss.[43–46] In a 'snapshot' assessment of 52–99 year olds, Rigters *et al.* ($n = 3315$) demonstrated significantly increased prevalence of high frequency hearing loss in both men (β coefficient, 3.01) and women (β coefficient, 2.49) and low frequency hearing loss in women (β coefficient, 1.69) in smokers compared with non-smokers.[43] Questionnaire-based studies have demonstrated a small but increased odds of developing hearing loss in smokers with a background of noise-induced hearing loss.[44–46] In one trial, smokers with a background of noise-induced hearing loss had almost 4 times the prevalence of hearing loss (95 per cent CI, 2.81–5.52) compared with non-smokers or noise-exposed individuals. This was increased compared with individuals who only smoked cigarettes (adjusted prevalence ratio, 1.39; 95 per cent CI, 1.07–1.81) and those only exposed to noise (adjusted prevalence ratio, 2.66; 95 per cent, 1.86–3.82) highlighting the possible combined harmful effect on cochlear dysfunction.[44]

Electronic cigarettes

Electronic cigarettes are a less harmful alternative to traditional cigarettes because they do not contain the same number of carcinogenic components of cigarettes. Because of their relative modernity and lack of long-term safety data, their use is not advocated in favour of other nicotine replacement therapies, but they are not discouraged as a smoking cessation tool according to NICE.[47] Early studies have demonstrated respiratory irritation and reduced lung cell viability, which poses concern for middle-ear health due to the shared ciliated columnar epithelial lining.[48]

To date, one *in vitro* investigation of electronic cigarette liquid solution on human middle-ear epithelial cells has been conducted by Song *et al.* In this study, starved human middle-ear epithelial cells were incubated for 24 hours with electronic liquids of a variety of flavours from different manufacturers. Electronic liquids were found to induce cytotoxic effects on these cells and reduce their viability from 100 per cent to 32–62 per cent. Moreover, increased cytotoxicity was seen with menthol and fruit flavoured electronic liquid.[49] However, the clinical implications of this are currently unclear, and it is likely that trials investigating the clinical impact of electronic cigarettes on ear disease will face similar challenges as those faced by trialists investigating the effect of cigarette smoking, in particular at risk of confounding bias.

Electronic cigarettes contain nicotine and therefore may impact graft neovascularisation during tympanoplasty. Song *et al.* demonstrated increased human middle-ear epithelial cell cytotoxicity when nicotine was included, with cell viability reducing from 100 per cent to 25–43 per cent suggesting nicotine may have a role in middle-ear mucosal disease. This effect may be reduced with lower concentrations of nicotine containing electronic liquids but this was not tested in this study.[49] Recent animal studies have demonstrated nicotine to have a direct deleterious effect on cochlear outer hair cells, with reports of distorted shape, heterochromatic nuclei and vacuolated cytoplasms.[50] Despite this, there are currently no data for the sole clinical implications of nicotine in otology in humans. Propylene glycol is a Food and Drug Administration approved solvent that is commonly used in the chemical and food industry. Prior animal studies in rodents demonstrated administration of large concentrations in the middle-ear space induced inflammatory granulation tissue, subsequent Eustachian tube dysfunction and tympanic membrane retraction and cholesteatoma formation.[51,52] Song *et al.* found increased human middle-ear epithelial cell cytotoxicity with propylene glycol suggesting that concentrations in electronic liquids may also contribute to middle-ear mucosal disease.[49] Similarly, there are no *in vivo* clinical data in humans for propylene glycol.

Amongst the adolescent and paediatric population, there is concern over electronic cigarettes acting as a gateway drug to nicotine addiction and cigarette smoking.[6] In the younger paediatric population, there is concern over accidental ingestion of the liquids. One case report found ingestion of electronic liquid solution led to bilateral SNHL with average thresholds of 63 dB for the right ear and 67 dB for the left ear.[53] This may be attributable to ethylene glycol, a constituent of anti-freeze solutions, which has been demonstrated to cause bilateral SNHL when ingested in extremely

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high concentrations in addition to other systemic effects.[54,55] At present however, the effect of ethylene glycol in small doses as seen in electronic cigarettes on human ear cells is unknown.

Conclusion

Cigarette smoking is associated with recurrent acute otitis media, OME and SNHL in children exposed to second-hand smoke. In adults, it is associated with active and aggressive CSOM, worse tympanoplasty success rates, increased post-operative complications and SNHL that is more pronounced in the long term and at high frequencies. Cigarette smoking can therefore be considered an important contributor to the global health burden of unaddressed hearing loss and more individual consequences of hearing loss, including poorer quality of life and social isolation. During otological surgery, graft uptake success rates may be improved with cartilage grafts. The effects of electronic cigarettes in otology are largely unknown, but early *in vitro* studies have demonstrated middle-ear epithelial cell toxicity is exacerbated by nicotine and propylene glycol. It is likely that large long-term observational trials of electronic cigarettes will be required to demonstrate their long-term effect as popularity rises.

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