Original article

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Exposure to loud noise and risk of vestibular schwannoma: results from the INTERPHONE international case–control study

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Objective Studies of loud noise exposure and vestibular schwannomas (VS) have shown conflicting results. The population-based INTERPHONE case–control study was conducted in 13 countries during 2000–2004. In this paper, we report the results of analyses on the association between VS and self-reported loud noise exposure.

Methods Self-reported noise exposure was analyzed in 1024 VS cases and 1984 matched controls. Life-long noise exposure was estimated through detailed questions. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using adjusted conditional logistic regression for matched sets.

Results The OR for total work and leisure noise exposure was 1.6 (95% CI 1.4–1.9). OR were 1.5 (95% CI 1.3–1.9) for only occupational noise, 1.9 (95% CI 1.4–2.6) for only leisure noise and 1.7 (95% CI 1.2–2.2) for exposure in both contexts. OR increased slightly with increasing lag-time. For occupational exposures, duration, time since exposure start and a metric combining lifetime duration and weekly exposure showed significant trends of increasing risk with increasing exposure. OR did not differ markedly by source or other characteristics of noise.

Conclusion The consistent associations seen are likely to reflect either recall bias or a causal association, or potentially indicate a mixture of both.

Key terms acoustic neuroma; epidemiology; noise exposure.

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Vestibular schwannoma (VS) or acoustic neuroma is a very rare, mostly benign tumor developing from the Schwann cells of the sheath of the eighth cranial nerve. It constitutes about 5–6% of all intra-cranial tumors and about 80% of cerebello-pontine angle tumors (1, 2). Incidence rates vary by country, ranging between 0.6–1.1 per 100 000 person-years, with similar rates in men and women (3, 4).

Most VS are non-familial and unilateral (5). Neurofibromatosis type 2, an autosomal dominant disease related to mutations in the NF2 gene, is associated with a small proportion of VS often with bilateral presentation (1). Other than elevated risks from exposure to high levels of ionizing radiation (6, 7), little is known about other exogenous risk factors that may be involved in the etiology of VS. Epidemiological investigations of smoking habits, occupations and occupational exposures, sociodemographic factors, cellular phone use, hormones, and allergic diseases have so far not established additional determinants of VS risk (8–19).

A possible association between loud noise exposure and VS has been investigated by several studies, with inconsistent findings (20–30). Of these, analyses based on self-reported exposures to noise have shown an increased odds ratio (OR) (24, 25, 27). Results for analyses combining self-reported occupational calendars with exposure levels from job-exposure matrices (JEM) have been inconsistent (22, 28). No association was seen in a large Swedish record linkage-based case–control study applying a noise-measurement based JEM (26).

The INTERPHONE study is an international multicenter case–control study involving 13 countries, coordinated by the International Agency for Research on Cancer (IARC), Lyon (29). The main goal of INTERPHONE was to explore cellular telephone use as a possible risk factor for central nervous system tumors including VS (13, 29); additionally, participants were asked about other exposures and life events, such as ionizing radiation, occupational and medical history, and, for VS, exposure to loud noise. Country-specific analyses of loud noise and VS risk have already been published for three INTERPHONE countries: Sweden, Germany and France (24, 25, 27). Some previous INTERPHONE publications used the term acoustic neuroma to refer to the same tumor here referred to as VS.

This report presents the results of the analyses of the association between vestibular schwannoma and self-reported loud noise exposure using the pooled multicenter INTERPHONE study, totaling 1024 VS cases and their 1984 matched controls.

Methods

Study design

INTERPHONE was conducted in 16 centers in 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway,

Sweden, and the UK) using a common core study protocol. Fieldwork was conducted between 1999 and 2005. Detailed descriptions of study methods have been reported elsewhere (14, 29, 30).

Participants

For the present analysis, we focussed on patients diagnosed with a schwannoma of the acoustic nerve (ICD-9 code 225.1, ICD-10 code D33.3, or ICD-O topography code C72.4 and morphology code 9560/0). Eligible cases were aged 30–59 years at diagnosis of VS and resident in the study regions during the study period of 2–4 years, depending on the center. Cases were ascertained mainly from neurological and neurosurgical facilities, from otorhino-laryngological units and local cancer registries. All diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. Ascertainment was done actively within treatment facilities. Completeness of ascertainment was checked through secondary sources, such as population- or hospital-based cancer registries, medical archives, pathological department files and hospital discharge or billing files.

Two controls were randomly selected for each case from the locally most appropriate population-based sampling frame, mainly population resident registries. Controls were either individually matched on age and sex, and, in Israel, on ethnic origin, or frequency matched during sampling with post hoc individual matching after ascertainment. In this report, we used the same sets of matched triplets as in the previously published analyses on VS and cellular telephone use (14), and the same reference dates, which, for cases, were the dates of diagnosis, and, for controls, the dates of diagnosis of their matched case.

Data collection

Participants were mainly interviewed in person (>99% cases, >99% controls) and face-to-face (95% cases, 94% controls). Computer-assisted personal interviews were conducted in all centers except Finland. Cases were interviewed on average 9.8 months after diagnosis, and controls were interviewed 3.4 months later than cases, on average.

Participants were asked a sequence of screening, and, if applicable, detailed questions about their lifetime exposure to loud noise at work, in leisure and from the environment (see supplementary material, www.sjweh.fi/show_abstract.php?abstract_id=3781). In Canada, France and Sweden, participants were shown a diagram of sound levels to assist them in answering the questions. In Japan, participants were not systematically asked all questions concerning loud noise at work; therefore, the 82 cases and 137 controls from this country were excluded from this report.

In addition, the questionnaire included sections on sociodemographic factors (marital status, educational level), smoking habits, and presence of medical conditions including hearing loss, tinnitus (defined as serious buzzing or ringing in the ears), diagnosed neurofibromatosis and tuberous sclerosis.

Statistical methods

Conditional logistic regression for matched sets (two controls per case) was used to estimate OR and their 95% confidence intervals (CI). Analyses were conducted with and without adjustment for the following potential confounders: educational level, marital status and smoking patterns (never, past, current smoker). The results of the adjusted analyses were reported throughout; the differences between adjusted and unadjusted estimates were ≤0.1, except for center-specific results and results stratified by hearing symptoms. When numbers permitted, OR were calculated for men and women separately.

Analyses were performed separately for exposure at work and during leisure time, as well as for total exposure with exposure lagged by periods of 1, 5 and 10 years prior to the reference date. These lag periods (ie, latency period between exposure and disease) have been previously used in analyses of VS risk in the INTERPHONE study. The reference group consisted of participants who did not report that they had been exposed to loud noise up to 1 year before their reference date, at work, during leisure time, or both as appropriate. Living for >10 years in a noisy environment was also investigated in relation to VS risk.

Continuous variables, derived from the subject responses, were categorized into tertiles, and rounded as follows: time since first exposure (<20, 20–29, ≥30 years), duration of exposure (0–5, 6–19, ≥20 years) and age at first exposure (≤18, 19–24, ≥25 years old). When linear trend tests on ordered variables were performed, the non-exposed subgroup was the reference (coded 0) and the exposed categories were coded 1, 2, or 3. Amount of exposure was evaluated by combining the frequency (hours per week) and duration (years) of exposure.

Following Edwards and colleagues (23), sources of noise were categorized by an occupational physician from UMRESTTE, Lyon, France, expert in noise assessment, as follows: construction work, machines, power tools; motors (airplanes, car racing); music (including employment in music industry); high-volume noise from humans (such as shouting or yelling at sports events, or day care centers) or animals (such as cattle); shooting or explosions; mixed sources, (ie, noise exposure histories with more than one of the previous sources); and other sources (Massardier-Pilonchéry A, personal commnica-

tion). The last category included sources that could not be classified due to imprecision or that were evaluated as leading to exposures <80 acoustic decibels but had been reported by the interviewee as loud noise.

Participants with missing values for the exposure variables were excluded from analyses, which could lead to exclusion of their matched controls or case. Missing values for adjustment variables constituted a separate category.

Sensitivity analyses were carried out: (i) with the reference category including only participants explicitly stating that they had never been exposed to loud noise and no lag period (ii) with a lag period of 5 years; (iii) excluding telephone and proxy interviews; (iv) excluding persons with co-morbidity of neurofibromatosis or tuberous sclerosis, or bilateral tumors, given that their exposure disease association might differ from that of the rest of the population; (v) stratified according to the case's type of auditory symptoms (no symptom, hearing loss only, or tinnitus with or without hearing loss), as these may impact participants' noise perception and recall; and (vi) treating periods of exposure during which protective equipment was used most of the time as unexposed time.

The ethics committees of all involved centers and of the IARC approved this study. Informed consent was obtained from all study participants. The authors followed the Declaration of Helsinki's principles.

Results

Altogether 1279 VS cases were eligible for this study, of whom 146 declined to participate in the interview, 5 had died or were too ill to undertake an interview and no proxy could be found, 12 were not approached as requested by their treating physician, and 12 did not speak the respective center-specific interview languages. In addition, research teams could not trace 46 cases and 6 were not interviewed for other reasons, leaving 1052 cases completing the interview (82% participation). Among eligible controls, 53% participated, 30% refused and 17% did not participate for other reasons. In addition, 16 cases for whom no matching control was found, 9 who were not asked the loud noise questions, 3 who did not know if they had ever been exposed to loud noise, and their 20 matched controls could not be included, leaving 1024 VS cases and 1984 controls for analyses of the associations between VS and noise exposure.

Most VS were histologically verified (76% of the interviewed cases), with 17% diagnosed by imaging only (computed tomography or magnetic resonance imaging scans). All but three tumors were unilateral. The occurrence of VS was comparable on both sides of the

Table 1. Distributions of selected characteristics of vestibular schwannoma cases and controls in the risk analyses of loud noise exposure: International Interphone Study, 2000–2004.

	Cases		Controls	
	N	%	N	%
Sex				
All	1024	100	1984	100
Men	501	49	963	49
Women	523	51	1021	51
Age at diagnosis/reference date (years)				
<40	213	21	393	20
40–49	348	34	688	35
≥50	463	45	903	46
Countries				
Australia	127	12	254	13
Canada	83	8	166	8
Denmark	68	7	135	7
Finland	74	7	143	7
France	106	10	208	10
Germany	64	6	124	6
Israel	70	7	138	7
Italy	30	3	60	3
New Zealand	16	2	19	1
Norway	38	4	75	4
Sweden	102	10	197	10
UK North	94	9	170	8
UK South	152	15	295	15
Type of interview				
Face to face, self/partly proxy	974	95	1862	94
Telephone, self/partly proxy	47	5	117	6
Face to face or telephone, proxy	3	0	5	0
Marital status [a]				
Single	91	9	201	10
Married or living with someone	812	79	1538	78
Separated, divorced, widowed	118	12	244	12
Education [b]				
High	278	27	587	30
Medium	312	30	592	30
Low	432	42	801	40
Regular smoking [c]				
Current and past smokers	460	45	1070	54
Never smokers	563	55	912	46
Ever exposed to loud noise				
Yes	579	57	941	47
No	445	43	1043	53
Lived >10 years in noisy environment				
Yes	68	7	116	6
No	952	93	1843	94
Hearing loss [d]				
Yes	849	83	408	21
No	167	16	1544	78
Tinnitus [e]				
Yes	626	61	224	11
No	389	38	1731	87
Neurofibromatosis [f]				
Yes	6	1	1	0
No	1016	99	1982	100
Tuberous sclerosis [g]				
Yes	0	0	1	0
No	1022	100	1982	100

[a] Data are missing for 3 cases and 1 control.

[b] High=university or postgrad. Univers.; medium= secondary/professional/high level techn. school; low= 3yr techn. training or secondary school; (categories are country-specific, presented in details elsewhere(29)); data are missing for 2 cases and 4 controls.

[c] Data are missing for 1 case and 2 controls.

[d] Data are missing for 8 cases and 32 controls.

[e] Data are missing for 9 cases and 29 controls.

[f] Data are missing for 2 cases and 1 control.

[g] Data are missing for 2 cases and 1 control.

head (50% on the left versus 47% on the right); laterality information was missing for 3% of eligible cases.

Selected characteristics of cases and controls are presented in table 1; 49% of the cases were men, 51% were women, and approximately equal numbers < and >50 years old. The percentage of subjects contributed by different centers varied from 2% in New Zealand to 15% in Southern UK. There were more smokers among controls (54%) than cases (45%). The proportion of controls having the highest educational level was hardly higher than for cases (30% among controls, 27% among cases).

Auditory symptoms were common amongst cases with 83% of cases reporting hearing loss and 61% tinnitus. Symptoms were markedly less common among controls, with 21% reporting hearing loss and 11% tinnitus. Six cases and one control reported having neurofibromatosis, and one control reported having tuberous sclerosis. In reponse to the question "have you ever been exposed to loud noise?" 579 cases (56.5%) and 941 controls (47.4%) responded in the affirmative, giving an OR of 1.5 (95% CI 1.3–1.8). Living for >10 years in a noisy environment showed an adjusted OR of 1.2 (95% CI 0.9–1.7).

Table 2 presents the sex-specific results for reported occupational and leisure noise exposure, separately and combined, for different lag periods. The OR for total exposure was 1.6 (95% CI 1.4–1.9) using a 1-year lag; for 5- and 10-years lag periods, OR of 1.6 (95%CI 1.4–1.9) and 1.7 (95%CI 1.4–2.1) were observed. Using a 1-year lag, the OR associated with only occupational noise was 1.5 (95% CI 1.3–1.9), with only leisure noise 1.9 (95% CI 1.4–2.6), and with both, 1.7 (95% CI 1.2–2.2). The OR were slightly higher for longer lags among women or when disregarding exposure during periods of use of protective equipment (not shown), though the respective confidence intervals overlapped substantially. Associations were similar amongst men and women.

Analyses of the associations between VS and occupational noise are presented in tables 3 and 4, and in supplemental figure 1 (www.sjweh.fi/show_abstract.php?abstract_id=3781). Compared to participants having no occupational noise exposure, OR increased slightly with increasing lag time, with an OR of 1.6 (95% CI 1.3–1.9) for 10-years lag time (data not shown). They also increased with increasing time since first exposure (P<0.001), duration of exposure (P<0.001) giving, for ≥20 years of exposure, an OR of 1.9 (95% CI 1.4–2.5), and with amount of exposure. In nearly all center-specific analyses, OR increased with increasing time since first exposure (supplemental figure 1A, www.sjweh.fi/show_abstract.php?abstract_id=3781) but not with duration (supplemental figure 1B, www.sjweh.fi/show_abstract.php?abstract_id=3781). All sources of occupational noise were associated with OR of similar magnitude, between 1.4–1.8 (table 4). Likewise, self-reported exposure to "other" sources, which included sources that experts did not rate as resulting in high noise exposure also produced elevated OR.

Similarly, noise exposure during leisure time activities showed elevated OR (tables 3 and 4). Compared with participants who did not mention leisure noise exposure, OR remained the same with increasing lag

Table 2. Odds ratios (OR) for vestibular schwannoma according to self-reported loud noise exposure at work or during leisure-time activities by gender and lag period: International Interphone Study, 2000–2004. [CI=confidence interval.]

	All participants						Men						Women					
	Cases (N=1024)		Controls (N=1984)		OR [a]	95% CI	Cases (N=501)		Controls (N=963)		OR [a]	95% CI	Cases (N=523)		Controls (N=1021)		OR [a]	95% CI
	N	%	N	%			N	%	N	%			N	%	N	%		
Work and/or leisure exposure [b, c]																		
Not exposed	546	53	1247	63	1.0		192	38	472	49	1.0		354	68	775	76	1.0	
Exposed during leisure only	82	8	113	6	1.9	1.4–2.6	44	9	58	6	2.0	1.3–3.2	38	7	55	5	1.6	1.0–2.6
Exposed at work only	296	29	476	24	1.5	1.3–1.9	185	37	324	34	1.5	1.2–2.0	111	21	152	15	1.6	1.2–2.2
Exposed at work and in leisure	98	10	143	7	1.7	1.2–2.2	79	16	106	11	1.9	1.3–2.7	19	4	37	4	1.2	0.7–2.2
Total occupational and leisure noise by duration of lag period [b]																		
Not exposed before 1-year lag period	546	53	1247	63	1.0		192	38	472	49	1.0		354	68	775	76	1.0	
Exposed before 1-year lag period	476	47	732	37	1.6	1.4–1.9	308	62	488	51	1.7	1.3–2.1	168	32	244	24	1.6	1.2–2.0
Not exposed before 5-year lag period	563	55	1281	65	1.0		201	40	482	50	1.0		362	69	799	78	1.0	
Exposed before 5-year lag period	459	45	698	35	1.6	1.4–1.9	299	60	478	50	1.6	1.3–2.0	160	31	220	22	1.7	1.3–2.1
Not exposed before 10-year lag period	586	57	1344	68	1.0		212	42	509	53	1.0		374	72	835	82	1.0	
Exposed before 10-year lag period	436	43	635	32	1.7	1.4–2.1	288	58	451	47	1.6	1.3–2.1	148	28	184	18	1.9	1.4–2.5

[a] Conditional logistic regression matched by center, age, sex, and adjusted for education, smoking and marital status.

[b] Exclusions: 2 cases (1 man, 1 woman) and 1 male control with incomplete interview, and 4 controls (2 men, 2 women) matched to the 2 cases.

[c] All exposures are truncated to 1 year before reference date.

Table 3. Odds ratios (OR) for vestibular schwannoma according to loud noise exposure by exposure status, time since first exposure, duration, amount of exposure and age at first exposure: International Interphone Study, 2000–2004. [CI=confidence interval.]

	Exposure at work						Exposure during leisure time					
	Cases		Controls		OR [a,b]	95% CI	Cases		Controls		OR [a,c]	95% CI
	N	%	N	%			N	%	N	%		
Exposure status												
Not exposed	625	61	1354	69	1.0		835	21	1693	22	1.0	
Exposed	394	39	614	31	1.4	1.2–1.7	178	4	255	3	1.5	1.2–1.8
Time since first exposure (years)												
0	625	61	1354	69	1.0							
<20	127	12	248	13	1.1	0.8–1.4						
20–29	125	12	179	9	1.5	1.2–2.0						
≥30	142	14	187	10	2.0	1.5–2.6						
Trend test P-value					<0.001							
Duration of exposure (years)												
0	625	61	1354	69	1.0		835	82	1693	87	1.0	
0–5	116	11	200	10	1.3	1.0–1.7	51	5	76	4	1.5	1.0–2.2
6–19	160	16	265	13	1.4	1.1–1.7	75	7	91	5	1.7	1.2–2.3
≥20	118	12	149	8	1.9	1.4–2.5	52	5	88	5	1.2	0.8–1.8
Trend test P-value					<0.001						0.005	
Amount of exposure												
Not exposed	625	61	1354	69	1.0							
Exposed, low amount [d]	194	19	315	16	1.3	1.1–1.7						
Exposed ≥10 hours/ week for >5 years	200	20	299	15	1.6	1.3–2.0						
Not exposed	625	61	1354	69	1.0							
Exposed, low amount [e]	277	27	458	23	1.3	1.1–1.6						
Exposed > 20 hours/ week for >10 years	117	11	156	8	1.8	1.4–2.4						
Age at first exposure (years)												
0	625	61	1354	69	1.0		835	82	1693	87	1.0	
<18	125	12	140	7	2.0	1.5–2.7	80	8	113	6	1.5	1.1–2.0
18–24	128	13	258	13	1.1	0.9–1.4	48	5	76	4	1.4	0.9–2.0
≥25	141	14	216	11	1.5	1.2–1.9	50	5	66	3	1.6	1.1–2.3

[a] The reference category consists of subjects who were not exposed 1 year before the reference date. OR from conditional logistic regressions with subjects matched by center, age and sex, and adjusted for education, smoking, and marital status.

[b] 5 cases with missing data and their 10 matched controls, and 6 additional controls with missing data were excluded from these analyses.

[c] 7 cases with missing data including 3 with dates missing, and 4 cases whose matched controls (n=6) had missing data, and 24 controls who did not know (including 4 with dates missing) and 12 controls matched to the cases who did not know were excluded from these analyses.

[d] The intermediate category consists of subjects who were exposed, but not to ≥10 hours/week for > 5 years.

[e] The intermediate category consists of subjects who were exposed, but not to >20 hours/week for >10 years.

time with an OR of 1.5 for a 10-year lag (data not shown). Although the OR for ≥20 years of leisure noise exposure was 1.2 (95% CI 0.8–1.8), a significant increasing trend (P=0.005) was observed with increasing duration; a similar pattern was seen with time since first exposure. There was little variation in OR according to age at first exposure to leisure noise. Exposure to music was the most commonly reported source of exposure during leisure. It resulted in an OR of 1.7 (95% CI 1.3–2.3). Exposure to noise from motors and tools also resulted in elevated OR. Leisure exposure to explosive noise such as shooting did not show any elevation in the OR (OR 0.8, 95% CI 0.5–1.5). Numbers in all these categories were small, however.

In sensitivity analyses, results did not substantially change when limited to subjects who stated they had never been exposed to loud noise as the reference category, ie, also not exposed during the 1-year lag time, when a 5-year lag was considered, when excluding proxy and telephone interviews, or when excluding subjects with neurofibromatosis, tuberous sclerosis and bilateral tumors (data not shown).

When compared with their respective controls, the subgroup of cases who reported tinnitus had elevated OR, and strong exposure–outcome trends (supplementary table S1, www.sjweh.fi/show_abstract.php?abstract_id=3781). In contrast, equivalent analyses restricted to cases with hearing loss but no tinnitus and their controls, produced lower OR and inconsistent associations; the smaller numbers in the subgroup of cases with normal hearing made these analyses more difficult to interpret. When periods during which the participant reported using hearing protection devices most of the time were treated as periods of no exposure, similar overall associations were found.

Table 4. Odds ratios (OR) for vestibular schwannoma according to source and characteristics of noise exposure: International Interphone Study, 2000–2004. [CI=confidence interval; NA=not available.]

	Exposure at work						Exposure during leisure time					
	Cases		Controls		OR [a,b]	95% CI	Cases		Controls		OR [a,c]	95% CI
	N	%	N	%			N	%	N	%		
Source of exposure												
Not exposed	625	61	1354	69	1.0		835	82	1693	87		
Machines, power tools, and/or construction	265	26	428	22	1.4	1.1–1.7	23	2	26	1	1.5	0.8–2.8
Motors, including airplanes	86	8	143	7	1.4	1.0–1.9	20	2	26	1	1.5	0.8–2.8
Music	33	3	44	2	1.7	1.1–2.8	96	9	128	7	1.7	1.3–2.3
Animal noise, children, sport, restaurants, bars	29	3	40	2	1.6	0.9–2.7	3	0	4	0	1.8	0.4–8.5
Explosions	29	3	42	2	1.5	0.9–2.5	17	2	40	2	0.8	0.5–1.5
Several sources [d]					NA		17	2	26	1	1.3	0.7–2.5
Other [e]	21	2	27	1	1.8	1.0–3.3	2	0	5	0	0.9	0.2–5.0
Character of noise exposure at work throughout life [f]												
Not exposed at work	625	61	1353	69	1.0							
Intermittent	121	12	184	9	1.5	1.1–2.0						
Persistent	180	18	293	15	1.4	1.1–1.7						
Powerful	34	3	54	3	1.5	0.9–2.3						
Intermittent and powerful	7	1	9	0	1.8	0.6–5.2						
Persistent and powerful	10	1	11	1	1.7	0.7–4.2						
Persistent and intermittent	28	3	43	2	1.5	0.9–2.5						
Persistent, intermittent and powerful	12	1	15	1	1.9	0.9–4.1						

[a] The reference category consists of subjects who were not exposed 1 year before the reference date. OR from conditional logistic regressions with subjects matched by center, age and sex, and adjusted for education, marital status and smoking status.

[b] Multiple assessments are possible. 5 cases with missing data and their 10 matched controls, and 6 additional controls with missing data were excluded. Reference category: not exposed at work.

[c] Multiple assessments are not possible. 7 cases with missing data including 3 with dates missing, and 4 cases whose matched controls (n=6) had missing data, and 24 controls who did not know (including 4 with dates missing) and 12 controls matched to the cases who did not know were excluded from this analysis. Reference category: not exposed during leisure time.

[d] Participants with several exposure sources, except those with one source of exposure and a source classified as "Other", which were included in the respective source.

[e] Left panel: includes occupational exposure reported by subject such as "noise from work", that could not be categorised more precisely, also includes sources assessed by expert as not leading to occupational loud noise exposure, such as "telephone constantly ringing". Right panel includes leisure time exposures reported by subject but unclear if exposed, such as "vacuum cleaner".

[f] Additional missing data on this variable for 2 cases and 3 controls and 3 matched controls; these subjects were excluded from these analyses.

Discussion

In this study of 30–59-year-old adults, we found consistent associations between VS and self-reported exposure to loud noise, with almost all the exposure metrics considered. For occupational exposures, time since first exposure, duration of exposure, amount of noise exposure, and earlier age at first exposure showed exposure–response associations; risk estimates did not appear to vary by the source or other characteristics of noise. Similar associations were observed for men and women. The increasing OR by increasing time since first occupational exposure were found in all study centers, although not always at the same magnitude. OR by duration of exposure were much less consistent across centers. Associations did not appear to depend much on the choice of lag period (1, 5 or 10 years). Exposure during leisure activities produced similar, but less consistent associations than occupational exposures, except for explosive noise exposure. OR were not higher for participants exposed to both.

In summary, our results are in line with several publications on self-reported noise exposure and VS in different study populations (20–22, 28) but were not consistent with studies of occupational noise exposures assessed by JEM, which did not show such positive associations (26, 28).

One of the primary strengths of INTERPHONE is its sample size: it is the largest study published to date, in terms of VS case numbers, permitting various stratified analyses to be conducted with reasonable statistical power. All INTERPHONE centers followed a common core study protocol, permitting pooling of the original data. The investigation of heterogeneity across study centers showed a high level of consistency in results. The questionnaire elicited detailed information on loud noise exposure. Another strength of INTERPHONE is its population-based control group, but this approach resulted in lower participation by controls than cases, which is a possible limitation, as it might have introduced selection bias (as occurred in relation to previous results reported for mobile phone use in the same study) (31). Participation was greater by subjects with a higher

level of education, which may be associated with less occupational noise exposure. Although the analyses were adjusted for education to limit the effect of the potential selection bias on the results, the possibility of a residual spurious increase of the OR remains.

The most likely explanations, however, of the elevated OR in our study is that either they reflect a true causal relationship between VS and loud noise exposure or that they are due to recall bias. Although a mix of these explanations is also a possibility, for clarity, we will discuss them separately as competing explanations.

Recall bias is a highly plausible explanation of the elevated OR. In two validation studies conducted within the German and French VS cases and controls of INTERPHONE, self-reported occupational noise exposure was compared to objective noise assessment. The occupational histories combined with JEM- or expert evaluation of noise levels showed satisfactory but not very good agreement with the self-reported occupational noise exposures in the 285 German and 328 French participants (Kappa coefficients of agreement of ≤0.58) (32 and Deltour et al. Validation of self-reported occupational noise exposure in participants of a French case–control study on acoustic neuroma. Submitted to Int Arch Occup Environ Health), also leaving the question open of what would be the real gold standard given that noise may vary considerably within the same profession. While the error related to JEM may more likely dilute an association, if it exists, the self-reported data may inflate weak associations or create spurious associations if differential between cases and controls. The validation studies show no substantial differential error, but this would not rule out weak spurious associations. Cases were more likely to report their noise exposure like the JEM or the expert evaluation than controls. Underreporting of exposed job episodes by controls would be expected to inflate OR for all exposure metrics, especially duration and amount of exposure, as well as sources and characteristics which were follow-up questions. No validated JEM was available to apply to our multinational study. The similarity of occupational and leisure noise exposures is intriguing. There is little objective data on leisure noise exposures (33, 34) and therefore it is difficult to compare levels of occupational to leisure noise exposure. Sources of noise are perhaps not dissimilar; although the levels of noise exposure in leisure activities might be higher, the duration of exposure is anticipated to be generally shorter than for occupational exposures. Moreover the impact of hearing protection devices is difficult to appreciate: while it is mandatory to wear them in certain occupational settings, they are not always fully efficient (35) and not necessarily always worn by the worker. For cases, recall differences may emerge during the period between first symptoms and final medical diagnosis: the median diagnostic delay for VS has been evaluated to be 14 months in a small Finnish study (N=59) (36). Interest of a physician in the patient's life-long loud noise exposures for a person with hearing disorders or diagnostic tests may have contributed to a heightened awareness of noise issues among cases. Associations with loud noise exposure were found primarily for VS patients who also reported tinnitus but not within those with hearing loss only or no auditory symptoms. Since tinnitus appears associated to noise (37, 38) and could sensitize patients to loud noise exposures, this may influence awareness and reporting of noise exposure. In addition, the conduct of the interview was long, and we cannot rule out that some participants, especially controls, got impatient, which might have led them to shorten the questioning by responding with "no" to some questions, thus contributing to recall and/or reporting bias.

Detection bias – whereby people occupationally exposed to noise are under more intense medical surveillance than the general population – might also induce exposure–response associations: exposure triggers the incidental diagnosis of VS (39, 40). This bias is expected to produce higher OR for more recent work periods but this pattern was not evident with respect to our analyses. We furthermore could not come up with a plausible mechanism for confounding by known causal factors to explain our results.

The associations observed in our study might also reflect a biological mechanism relating to initiation or promotion. Loud noise can damage hearing through acoustic trauma. Whether this could lead to cellular hyperplasia and tumor occurrence is not known, as the biological mechanisms underlying the development of VS are not well understood at present (41, 42). VS is generally a slow-growing benign tumor, but other growth patterns are also reported (43, 44). It is unlikely that noise induces direct DNA damage, but epigenetic mechanisms could affect promotion or initiation, via free radicals, the potential activation of p53 signaling pathway, or other mechanisms (45–48). Experimental studies in rodents, pigs and sheep showed that severe acoustic trauma (such as impulse noise) caused mechanical damage to the eighth cranial (vestibulocochlear) nerve and the surrounding tissue (49). Physiological disruptions of neurons along the auditory neuraxis, affecting intracellular signaling pathways and metabolism following damage have been reported (50). The relationship, if any, with the nerve sheaths is unclear, and no explanation for the location of most VS on the vestibular portion of the nerve is available at present (51).

If this hypothesis was correct, exposure misclassification due to broad job codes in JEM-based noise assessment might have reduced the OR to values that cannot be distinguished from 1.0 in studies using such approach.

In conclusion, using INTERPHONE, the largest case–control study of VS, an association between self-reported loud noise exposure and VS was shown, fairly consistent with the investigated exposures characteristics and sources, and for both sexes. The validation studies conducted in France and Germany within the framework of INTERPHONE permitted some evaluation of the level of recall bias. For this particular question, results suggest an underreporting of exposure among controls, and, consequently, inflation of the association. Further investigation is required on the extent of recall bias and on uncertainties in JEM assessments to determine which epidemiological design and exposure assessment method would be best for future studies, and on the biological mechanisms that might explain this epidemiological association between VS and loud noise exposure.

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Conflict of interest

The authors declare no conflicts of interest.

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