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The natural history of tinnitus in adults: a cross sectional and longitudinal analysis

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Abstract

Objective

To assess incidence and changes in tinnitus and bothersome tinnitus as well as associated risk factors in a large sample of UK adults.

Design

Prospective cohort study

Setting

United Kingdom

Participants

For cross-sectional analysis, a group of 168,348 participants aged between 40 to 69 years with hearing and tinnitus data, from the UK Biobank resource. Longitudinal analysis included a subset of 4,746 people who attended a 4 year retest assessment.

Main outcome measures

Presence and bothersomeness of tinnitus.

Results

17.7% and 5.8% of participants reported tinnitus or bothersome tinnitus respectively. The 4 year incidence of tinnitus was 8.7%. Multivariate logistic regression models suggested that age, hearing difficulties, work noise exposure, ototoxic medication, and neuroticism were all positively associated with both tinnitus and bothersome tinnitus. Reduced odds of tinnitus, but not bothersome tinnitus was seen in alcohol drinkers versus non-drinkers. Male gender was associated with increased odds of tinnitus, whilst female gender was associated with increased odds of bothersome tinnitus. At follow up, of those originally reporting tinnitus, 18.3% reported no tinnitus. Of those still reporting tinnitus, 9% reported improvement, 9% reported tinnitus becoming more bothersome, with the rest unchanged. Male gender and alcohol consumption were associated with tinnitus being reported less bothersome, hearing difficulties were associated with the odds of tinnitus being reported as more bothersome.

Conclusions

This study is one of the few to provide data on the natural history of tinnitus in a non-clinical population, suggesting that resolution is relatively uncommon, with improvement and worsening of symptoms equally likely. There was limited evidence for any modifiable lifestyle factors being associated with changes in tinnitus symptoms. In view of the largely persistent nature of tinnitus, public health strategies should focus on i) primary prevention and ii) managing symptoms in people that have tinnitus, and monitoring changes in bothersomeness.

Keywords

Tinnitus, Biobank, natural history, incidence

Article Summary

Strengths and limitations of this study

- This study investigated both the prevalence and incidence of tinnitus and its correlates in a sample drawn from the UK Biobank resource.
- The study includes both a cross sectional analysis of a large sample (168,348 participants), with the longitudinal component based on a smaller sample (4,746 participants).
- The UK Biobank resource, from which the data was drawn, is not completely representative of the UK population.
- A wide range of relevant risk factors were available for the analysis.
- Lack of a consensus on the definition of tinnitus hampers comparison across the literature.

Introduction

Tinnitus (the subjective experience of sound perception when there is no external source) can be a troublesome experience, and when severe can be associated with insomnia, poor concentration, anxiety, and/or depression.(1) Around 10-15% of adults have tinnitus, and although cost effective, the cost of care of patients with tinnitus is high.(2) The question of the natural history of tinnitus in adults is of major importance for both patients and clinicians (3) but data regarding the natural history of tinnitus in adults are scant. A few studies have investigated tinnitus in various populations longitudinally (Table 1). Estimates of the incidence of tinnitus vary depending on the age of the population and the definition of tinnitus in each study. Such studies are useful in demand forecasting for diagnostic and therapy services, but do not support the counselling of existing tinnitus cases regarding their prognosis. The main limitation of many studies examining changes in tinnitus over time is that they were conducted with specific populations, clinical samples, or with people taking part in tinnitus research, and so may not be representative of the general population.

Clifford et al. (4) reported on the progression of tinnitus in a US Marine cohort, indicating that worsening tinnitus was associated with the presence of Post-Traumatic Stress Disorder, and moderate/severe Traumatic Brain Injury (TBI). One other study reported a modest improvement in the bothersomeness of tinnitus at follow up 4.9 years after treatment by a Clinical Psychologist, the majority (59%) having received cognitive behaviour therapy for tinnitus.(3) Another study reported that severity of symptoms tended to be more severe, with tinnitus of longer duration among patients presenting for tinnitus therapy.(5) A systematic review and meta-analysis reporting the experiences of patients with tinnitus who were research participants enrolled in control (waiting list) arms of clinical trials reported a small, statistically significant improvement in tinnitus symptoms over time, though clinical significance of these improvements was unclear.(6) Placebo groups in controlled clinical trials of tinnitus treatments have also reported reduced bothersomeness of tinnitus immediately and up to 14 weeks post placebo treatment.(7-9) In a conference report Smith and Coles(10) reported data regarding tinnitus from the UK National Study of Hearing.(11) Participants reporting tinnitus experiences were asked to retrospectively rate their tinnitus loudness and annoyance at two stages of their tinnitus experience: ‘onset to middle’ and ’middle/recent or end’. These ill-defined sample points render the data in this report are

hard to interpret, but it appears that in a small number (8.5%) the tinnitus had resolved completely, and that there was a general trend over time towards decreased annoyance.

Large scale data regarding longitudinal experiences of a general population regarding tinnitus has not been reported to date, with the closest examples examining samples an order of magnitude smaller than the present study.(12, 13) The only large scale population data available examined only incidence and utilised indirect measures of tinnitus based on clinical record or health claim data. (14, 15) In the present study the aim was to establish the proportions of people who experience tinnitus and bothersome tinnitus, and changes in tinnitus and bothersome tinnitus over time and to determine demographic, health and lifestyle correlates, in order to inform patient counselling and identify potential avenues for prevention and treatment of tinnitus.

Table 1. Prevalence and incidence rates of tinnitus

Study	Definition of tinnitus	Population	Tinnitus Baseline	Follow-up interval
Gopinath, McMahon (13)	Tinnitus over the past year lasting 5 minutes or longer	Australia Age: >=55 years Baseline (n=2006) Follow-up (n=1292, female=58.9%)	37% (481)*	**5 year follow-up** Persisting: 82% (346) Resolved: 18% (78) Incident: 18% (156)
Nondahl, Cruickshanks (12)	Tinnitus over the past year of i) at least moderate severity or causing difficulty with sleep ii) mild tinnitus not affecting sleep	United States Age: 48-92 years Baseline (n=3753, female=57.7%) Follow-up (n=2800, female=58.6%)	8.2% (moderate tinnitus) (308)	**5 year follow-up** Incidence of significant tinnitus: 5.7% (143)
			20.2% (mild tinnitus) (754)	**5 year follow-up** Persisting : 68.6% (394) Resolved : 31.4% (180)
Nondahl, Cruickshanks (16)	Tinnitus over the past year of at least moderate severity or causing difficulty with sleep	United States Age: 48-92 years Follow-up (n=2922, female:59.3%)	Baseline N.A.	**10 year follow-up** 12.7% (371)
Lee, Do Han (14)	Based on record of health service utilisation for 'tinnitus' through the	South Korea Age: all ages Follow-up (n=51	N.A.	**Yearly incidence** 8.26-9.49 per 1000 from 2006-

	Korean National Health Insurance Service	million, female= not reported)		2015 9.1% 10 year incidence
Martinez, Wallenhorst (15)	Any tinnitus: based on health service utilisation for 'tinnitus' gathered through the United Kingdom Clinical Practice Research Datalink Significant tinnitus: as above but with related follow up within 28 days. See Martinez for full definition (15)	United Kingdom Age: <=85 years Follow-up (n=4.7 million, female= 50.5%)	N.A.	**10 year follow-up** Incidence significant tinnitus 5.4 per 10,000 person years Incidence any tinnitus 47.3 per 10,000 person years

Methods

Participants

Participants were drawn from the UK Biobank, an international resource for studying the genetic, environmental and lifestyle causes of diseases of middle and older age.(17) Participant recruitment was conducted via the UK National Health Service and aimed to be as inclusive as possible of the UK population. In total, 9.2 million invitations were sent to recruit 503,325 participants who were aged between 40 to 69 years between 2006 to 2010, a response rate of 5.47%. The UK Biobank sample contains a higher proportion of females, people reporting White British ethnic background and people living in less deprived areas than the general population.(18) The UK Biobank sample is not representative of the UK general population, but the disease-exposure relationships are thought to generalizable due to the size and inclusiveness of the sample. Hearing and tinnitus measures were included part way through data collection, so information on tinnitus at baseline was available for 168,348 participants.

Participants attended an assessment centre where data on demographic, health, environmental and lifestyle factors were collected via computerised questionnaire along with physical measures including hearing testing during assessments of around 90 minutes in duration. Further information on procedures and the data collected is contained on the UK Biobank website (http://www.ukbiobank.ac.uk/). During 2012 and 2013, 17,819 participants attended a retest assessment, with a 21% response rate. All baseline measures

were repeated, including hearing and tinnitus. The mean retest interval was 4.3 years (range 2 to 7 years); retest tinnitus data were available for 4,746 participants. (For further details of the repeat assessment, see http://biobank.ctsu.ox.ac.uk/~bbdatan/Repeat_assessment_doc_v1.0.pdf). UK Biobank received ethical approval from the North West-Haydock National Research Ethics Committee (Ref 11/NW/0382), and all participants provided written informed consent.

Information on sex and ethnicity (based on 2001 UK Census categories) and area of residence was collected. Area of residence was used to determine a Townsend deprivation score. The Townsend deprivation score is a proxy for socioeconomic status, and is applicable across the countries of the UK.(19) Townsend scores are based on four variables; unemployment, non-car ownership, non-home ownership and household overcrowding. Each variable is normalised relative to national levels and summed to provide an overall deprivation index. Higher scores represent more deprived (less affluent) socioeconomic status. In the regression analyses below, Townsend scores were grouped from least to most deprived quartiles in the study sample.

Tinnitus

Participants were asked "Do you get or have you had noises (such as ringing or buzzing) in your head, or in one or both ears, that lasts for more than five minutes at a time?". In this analysis, tinnitus was identified based on responses of 'yes most of the time', 'yes a lot of the time' or 'yes some of the time', similar to criteria used in other studies of the epidemiology of tinnitus (20-22). If a participant reported that they did experience tinnitus that lasted for more than five minutes at a time, they were asked "How much do these noises worry, annoy or upset you when they are at their worst?"; severely, moderately, slightly or not at all. In this analysis, 'bothersome' tinnitus was identified on the basis of responses of either 'moderately' or 'severely'.

Incident tinnitus was identified if a person who did not report tinnitus at baseline reported tinnitus at least some of the time at retest. Among those who reported tinnitus at baseline, 'Worse tinnitus' was identified if someone reported their tinnitus as not being bothersome

at baseline (i.e. 'slightly' or 'not at all') but reported their tinnitus being bothersome at follow up (i.e. 'moderately' or 'severely').

Hearing

Participants completed an English version of the Digit Triplet Test (DTT), as test of speech recognition in noise developed for large scale hearing screening.(23, 24) The DTT correlates strongly with audiometric thresholds. The DDT is described elsewhere (http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100049). In short, fifteen sets of three monosyllabic digits (e.g. 6-1-3) were presented over circumaural headphones with the volume of presentation set to a comfortable level. Digits were presented in background noise shaped to match the spectrum of the spoken digits. Noise levels varied adaptively to track a SNR for the 50% recognition threshold, which was based on the mean SNR for the last eight triplets. Lower (more negative scores) indicate better performance. Hearing was additionally indexed by self-reported hearing status with the question "Do you have any difficulty with your hearing?".

Occupation- and music-related noise exposure, ototoxic medication, metabolic syndrome, physical activity, smoking, alcohol consumption and hearing aid use

The potential associations between tinnitus and risk factors were explored using a previously identified list and discussion between the authors.(1) Occupational and music-related noise exposure was assessed by the questions "*Have you ever worked in a noisy place where you had to shout to be heard?*" and "*Have you ever listened to music for more than 3 hours per week at a volume which you would need to shout to be heard or, if wearing headphones, someone else would need to shout for you to hear them?*"; with the response options (i) Yes, for more than 5 years (ii) Yes, for around 1 to 5 years (iii) Yes, for less than 1 year, (iv) No, (vi) Do not know, or (vii) Prefer not to answer. The criterion for work- and music-related noise corresponds to exposure exceeding 85 dB(A) (25). Use of ototoxic medication was identified on the basis of reported regular (daily, weekly or monthly) use of medications known to have ototoxic properties (including loop diuretics, aminoglycoside antibiotics, quinine derivatives, non-steroidal anti-inflammatories and salicylates). Metabolic syndrome was identified based on the Adult Treatment Panel III report of the National Cholesterol Education Program (ATP III NCEP) criteria;(26) positive risk was

identified on the basis of three or more of waist circumference of ≥102 cm in men and ≥88 cm in women; participant report of high cholesterol or if the participant reported they were currently taking medication for high cholesterol; measured systolic blood pressure greater than 130 mm Hg or diastolic pressure greater than 85 mm Hg; participant report of diabetes or the use of medication for diabetes. Participants were identified as being physically 'active' if they reported doing more than 10 minutes of physical activity in relation to the question "Yesterday, about how long did you spend doing activities that needed moderate effort, making you somewhat short of breath? For example walking upstairs, going to the gym, jogging, energetic dancing, aerobics, most sports, using heavy power tools and other physically demanding DIY & gardening." 'Inactive' participant were identified on the basis of physical activity of 10 minutes or less. Current or previous tobacco smoking was identified on the basis of positive responses to two questions; "Do you smoke tobacco now?" and "In the past, how often have you smoked tobacco?" Alcohol drinkers were identified on the basis of any report of current alcohol consumption ("About how often do you drink alcohol?"; 'Special occasions only', 'One to three times a month', 'One or twice a week', 'Three or four times a week' or 'Daily or almost daily'). Non-drinkers were categorised based on a response of 'Never'. Hearing aid use was identified on the basis of a 'yes' response to "Do you use a hearing aid most of the time?".

Neuroticism

Neurociticism scores were based on summed positive responses to 12 items from the Eysenck Personality Inventory (EPI),(27) including Does your mood often go up and down?; Do you ever feel 'just miserable' for no reason?; Are you an irritable person?; Are your feelings easily hurt?; Do you often feel 'fed-up'?; Would you call yourself a nervous person?; Are you a worrier?; Would you call yourself tense or 'highly strung'?; Do you worry too long after an embarrassing experience?; Do you suffer from 'nerves'?; Do you often feel lonely?; Are you often troubled by feelings of guilt?. Higher scores indicate greater neuroticism.

Data Analysis

Cross tabulations performed to describe characteristics of those who reported tinnitus versus no tinnitus, and the subset of people with tinnitus who reported 'bothersome' tinnitus. Demographic, health, lifestyle and psychological characteristics were selected on

the basis of previously being linked to tinnitus.(21, 28, 29) There were missing data for some measures primarily due to measures being added to the study protocol at different time points during data collection (see Table 2). Because the reason for the missing data was not systematically related to the outcomes of interest in this study, it was assumed that the data were missing completely at random. Missing variable analysis did not identify any pattern to the missing data. Multinomial logistic regression was used to model cross-sectional baseline associations between demographic, hearing, noise exposure, health and lifestyle factors and tinnitus (versus no tinnitus) and bothersome tinnitus (versus non-bothersome tinnitus). A Cox proportional hazard model was used to model the incidence of tinnitus and more bothersome tinnitus at 4 year follow-up. Analyses were performed with IBM SPSS version 23.(30)

Patient and public involvement

Patient and public involvement is reported according to the Guidance for Reporting Involvement of Patients and the Public (GRIPP) – short form 17. 1. Aim: UK Biobank consulted with stakeholders including the public at several times during the planning stages and post implementation to obtain guidance and feedback in relation to; consent, confidentiality, access, commercialisation, and oversight/monitoring. The conception of the project and its aim sprung directly from public enquiries fielded by the British Tinnitus Association a partner in this project. 2. Methods: For the UK Biobank, a key element in the public consultation process was an initial workshop which included 20 members of the public in the study target age range and 10 outside the target age range. Sessions key points were noted, and sessions tape recorded, a post workshop questionnaire was sent to all attendees, and to any stakeholders who were not able to attend the workshops in person (to increase representativeness). 3. Results: Public opinion across many areas addressed in the aims was diverse, a full report can be found at http://www.ukbiobank.ac.uk/public-consultation/ 4. Discussion: Public input influenced ethical considerations, access to data, the consent process, the commercialisation of the resource, and oversight/monitoring. 5. Reflections/critical perspective: Public and other stakeholder input into the study was essential to ensure public confidence in the study conduct, and to respond to public concerns with the resource. Whilst efforts were taken to consider public input, the diversity

of opinion meant that not all perspectives were equally influential on the UK Biobank's design and conduct.

Results

Cross-sectional analysis

In this sample of adults aged 40 to 69 years, 17.7% (n = 29,861) reported tinnitus and 5.8% (n = 9,751) reported bothersome tinnitus. Table 2 summarises the characteristics of participants who reported that they experienced tinnitus versus those who did not report tinnitus. Characteristics of those who reported tinnitus are broken down further with respect to whether participants reported their tinnitus as being bothersome or not bothersome.

Table 2. Sample characteristics

	No tinnitus	Tinnitus		
		Tinnitus (any)	Tinnitus Not bothersome	Tinnitus Bothersome
	N = 138,487	N = 29,861	N = 20,110	N = 9,751
Age (168,348)*	56.4 (SD 8.2)	58.7 (SD 7.58)	57.5 (SD 8.22)	58.0 (SD 7.78)
Sex (male; 168,348)	44.0%	52.80%	51.0%	45.70%
Social economic status score+ (168,079)	-1.12 (SD 2.92)	-0.99 (SD 3.01)	-1.02 (SD 3.00)	-0.66 (SD 3.16)
SRT better ear (157,574)	-7.43 (SD 1.62)	-7.07 (SD 1.96)	-7.26 (SD 1.80)	-6.91 (SD 2.13)
Hearing difficulties (168,348)	21.3%	56.4%	43.4%	63.3%
Work noise exposure (166,805)	20.5%	34.4%	32.2%	37.0%
Music noise exposure (165,977)	11.5%	16.6%	17.4%	18.5%
Physical activity (106,989)	71.1%	71.7%	71.5%	69.3%
Ototoxic medication (168,348)	39.2%	46.5%	44.6%	53.1%
Alcohol drinker (168,201)	91.5%	90.1%	91.2%	88.1%
Current or previous smoking (167,725)	43.9%	48.5%	47.4%	50.7%
Metabolic risk (168,348)	9.1%	12.0%	10.7%	13.3%
Neuroticism score (136,600)	3.98 (SD 3.22)	4.63 (SD 3.41)	4.44 (SD 3.33)	5.64 (SD 3.47)

*The number in brackets indicates the number of participants that completed each measure.
+Social economic status indexed by Townsend deprivation index score; lower (more negative) score indicate less deprived (more affluent) status

All variables were entered simultaneously into multi-variable logistic regression models for tinnitus (versus no tinnitus) and bothersome tinnitus (versus not bothersome) (Table 3). Similar patterns of association were observed for tinnitus and bothersome tinnitus. The

Nagelkerke r^2 was 0.143 for tinnitus and 0.067 for bothersome tinnitus. Older age, male sex, poorer speech recognition threshold, hearing difficulties, work noise exposure, music noise exposure, physical activity, regular use of ototoxic medication, and neuroticism were associated with tinnitus. Alcohol consumption was associated with lower odds of tinnitus. Female sex, most deprived social economic status, poorer speech recognition threshold, hearing difficulties, work noise exposure, ototoxic medication and neuroticism were associated with bothersome tinnitus. The sample included 1013 hearing aid users. The analyses were re-run to check for interactions with hearing difficulties and hearing aid use on tinnitus and bothersome tinnitus. There was no significant hearing aid by hearing difficulties interaction for tinnitus (OR 0.50 95% confidence interval 0.21 – 1.21, $p = 0.125$) or bothersome tinnitus (OR 0.87 95% confidence interval 0.18 – 4.18, $p = 0.888$).

Table 3. Cross-sectional correlates of tinnitus and bothersome tinnitus

	Tinnitus N=80,380 $\chi^2(15) = 7110.23$, $p < 0.001$				Bothersome tinnitus N=21,690 $\chi^2(15) = 912.89$, $p < 0.001$			
		95% C.I. for EXP(B)				95% C.I. for EXP(B)		
	Exp(B)	Lower	Upper	p	Exp(B)	Lower	Upper	p
Age	**1.03**	**1.03**	**1.03**	**0.000**	1.00	1.00	1.01	0.176
Sex (male)	**1.20**	**1.15**	**1.25**	**0.000**	**0.74**	**0.68**	**0.80**	**0.000**
Social economic status				0.294				0.023
First Quartile 1 (Reference)				-				-
Second Quartile	1.02	0.97	1.08	0.484	0.95	0.86	1.05	0.297
Third Quartile	0.98	0.93	1.04	0.480	1.03	0.93	1.14	0.587
Fourth Quartile (most deprived)	1.03	0.98	1.09	0.262	**1.11**	**1.00**	**1.23**	**0.043**
SRT better ear	**1.03**	**1.02**	**1.04**	**0.000**	**1.02**	**1.00**	**1.05**	**0.020**
Hearing difficulties (yes)	**3.75**	**3.60**	**3.90**	**0.000**	**2.07**	**1.92**	**2.23**	**0.000**
Work noise exposure (yes)	**1.40**	**1.34**	**1.47**	**0.000**	**1.15**	**1.06**	**1.25**	**0.001**
Music noise exposure (yes)	**1.39**	**1.31**	**1.47**	**0.000**	1.03	0.93	1.13	0.576
Physical activity (yes)	**1.05**	**1.00**	**1.09**	**0.038**	0.97	0.89	1.04	0.372
Ototoxic medication (yes)	**1.18**	**1.13**	**1.23**	**0.000**	**1.19**	**1.11**	**1.28**	**0.000**

Alcohol drinker (yes)	**0.87**	**0.80**	**0.93**	**0.000**	0.89	0.78	1.01	0.070
Current or previous smoking (yes)	0.99	0.95	1.03	0.500	1.04	0.97	1.12	0.300
Metabolic risk (yes)	1.05	0.98	1.12	0.210	0.97	0.86	1.09	0.601
Neuroticism score	**1.05**	**1.04**	**1.06**	**0.000**	**1.10**	**1.08**	**1.11**	**0.000**

Longitudinal analysis

A subset of participants (3997 people) who had completed the questions about tinnitus and the full set of correlates of interest were included in the longitudinal analysis, with a mean retest interval of 4.3 years (2-7 years range). There were 276 cases of incident tinnitus among the 3,177 people who did not report tinnitus at baseline; a 4 year incidence of 8.7%. The Cox proportional hazard model for incident tinnitus between baseline and 4 year follow-up was not statistically significant ($\chi^2(15) = 21.6$, $p = 0.119$). Among the 820 people who reported tinnitus at baseline and completed responses at follow-up, 150 reported no tinnitus at follow-up (including 63 who claimed never to have had tinnitus); 18.3% of people reporting tinnitus at baseline did not report tinnitus at follow-up. Hearing difficulties were associated with reduced likelihood of no tinnitus at follow-up (Table 4).

Table 4. Cox proportional hazard model for no tinnitus at follow-up (i.e. resolved tinnitus)

	Resolved tinnitus N=565 ($\chi^2(15) = 26.7$, $p = 0.031$)			
		95% confidence interval		
	β	Lower	Upper	*p*
Age	0.99	0.96	1.03	0.683
Sex (male)	0.96	0.62	1.47	0.841
Social economic status				0.558
First Quartile 1 (Reference)				-
Second Quartile	1.11	0.69	1.80	0.671
Third Quartile	0.72	0.39	1.30	0.273
Fourth Quartile (most deprived)	1.01	0.55	1.85	0.972
SRT better ear	0.98	0.88	1.10	0.735
Hearing difficulties (yes)	**0.48**	**0.32**	**0.74**	**0.001**
Work noise exposure (yes)	1.47	0.95	2.26	0.080
Music noise exposure (yes)	1.26	0.76	2.09	0.379

Physical activity (yes)	1.48	0.84	2.58	0.173
Ototoxic medication (yes)	0.83	0.55	1.25	0.383
Alcohol drinker (yes)	0.66	0.30	1.47	0.309
Current or previous smoking (yes)	1.19	0.79	1.78	0.399
Metabolic risk (yes)	0.66	0.35	1.25	0.203
Neuroticism score	1.05	0.99	1.12	0.101

Among the 1,039 people who completed questions about tinnitus annoyance at baseline and follow-up, 850 (81.8%) reported no change, 93 (9%) reported that their tinnitus was more bothersome and 93 (9%) reported their tinnitus being less bothersome.

In a Cox proportional hazard model, cases of tinnitus being reported as being more bothersome (versus those reporting no change) were associated with higher (poorer) better ear SRT, non-drinking and female gender (Table 5). The sample included 27 hearing aid users, and the model was re-run to check for an interaction with hearing aid use and speech reception threshold. The interaction was not statistically significant (OR 0.88, 95% confidence interval 0.67 – 1.14, $p = 0.337$). The model for reduced bothersomeness was not statistically significant $\chi^2(15) = 24.1$, $p = 0.063$.

Table 5. Cox proportional hazard model for tinnitus bothersomeness worse

	Bothersomeness worse N=404 $\chi^2(15) = 34.4$, $p = 0.003$			
		95% confidence interval		
	β	Lower	Upper	*p*
Age	0.98	0.93	1.04	0.481
Sex (male)	**0.44**	**0.22**	**0.86**	**0.017**
Social economic status				0.258
First Quartile 1 (Reference)				-
Second Quartile	1.66	0.80	3.48	0.176
Third Quartile	0.77	0.27	2.23	0.633
Fourth Quartile (most deprived)	0.77	0.27	2.19	0.621
SRT better ear	**1.13**	**1.02**	**1.27**	**0.026**
Hearing difficulties (yes)	2.01	0.96	4.20	0.063
Work noise exposure (yes)	1.41	0.71	2.83	0.329
Music noise exposure (yes)	1.15	0.50	2.63	0.738
Physical activity (yes)	0.88	0.39	1.96	0.752

Ototoxic medication (yes)	1.24	0.65	2.34	0.513
Alcohol drinker (yes)	**0.30**	**0.11**	**0.87**	**0.026**
Current or previous smoking (yes)	1.61	0.83	3.11	0.156
Metabolic risk (yes)	0.67	0.22	2.04	0.485
Neuroticism score	0.95	0.86	1.06	0.381

Discussion

In cross-sectional analysis, 17.7% of adults 40-69 years old reported tinnitus, with 5.8% reporting that tinnitus was bothersome. The 4 year incidence of tinnitus in this sample was 8.7%. The study offered some cause for optimism with respect to the natural history of tinnitus; around 18% of people who reported tinnitus at baseline did not report tinnitus at follow-up, an average of 4 years later. For those that continued to experience tinnitus, 81.8% reported that tinnitus bothersomeness was unchanged after 4 years, 9% reported tinnitus became worse (previously not bothersome, now bothersome), and in 9% better (previously bothersome, now not). The strengths of the study include the large inclusive sample, which was not derived from a specific tinnitus nor hearing study. The availability of longitudinal data was a significant strength. Longitudinal tinnitus data are available in a very small number of other studies. The use of standard tinnitus phenotype questions allowed comparison of these results with those of other studies. Although accounted for in the model, the variability in time elapsed at retest (2-7 years) may be a limitation. However the minimum of 2 years is longer than the period of most intervention studies and provides time to observe natural variation in tinnitus. In terms of patient counselling about long term prognoses for tinnitus, the 4 year mean follow up period limits the certainty of any opinion in relation to longer-term outcomes. Further, there is the possibility that a person may have received clinical help for tinnitus during the intervening years. Most people seek help within the first year of onset,(31) so this is unlikely to have been the case for a large proportion of participants here. Unfortunately, information about receiving clinical help and the duration of tinnitus was not available in this study.

Tinnitus correlates

Poorer hearing (better ear SRT and self reported hearing difficulties) was associated with the presence of tinnitus and bothersome tinnitus. Hearing difficulties were associated with

lower likelihood of resolved tinnitus and SRT with lower likelihood of tinnitus being less bothersome over time. But there was no relationship between SRT or hearing difficulties and incident tinnitus. A relationship between tinnitus and hearing loss is consistently reported (21, 32-35) with hearing loss being proposed as a trigger for tinnitus which then persists due to maladaptive plasticity in the central auditory and associated systems.(36) The lack of a relationship between hearing and incident tinnitus may be due to the much smaller sample for the longitudinal analysis versus the cross-sectional analysis. Work noise exposure was associated with prevalent tinnitus and bothersome tinnitus. Music exposure was associated with prevalent tinnitus. Noise exposure is the primary modifiable risk factor for tinnitus (33, 37, 38) and the pathophysiological impact can be either cochlear hair cell dysfunction, leading to a subjective hearing loss, and/or cochlear synaptopathy, the effects of which are more subtle.(39)

Alcohol consumption was associated with reduced odds of tinnitus, but not of bothersome tinnitus. Moderate alcohol consumption has been suggested to have a protective effect on hearing, perhaps via cardiovascular pathways. (40, 41) Other studies reported no association between alcohol consumption and tinnitus (42, 43), with one study reporting increased risk of tinnitus with alcohol consumption.(41) There are several difficulties with disentangling the effect of alcohol consumption on tinnitus. First, alcohol consumption is highly confounded with socio-cultural factors that may also impact on health, including hearing.(44) Second, impacts of alcohol consumption may be dose-dependent; heavy alcohol consumption is certainly bad for general health, including hearing.(45) Impacts may be different for moderate or light levels of consumption.(45-47) Third, comparing health outcomes in drinkers versus non-drinkers may give the false impression that alcohol consumptions is linked to better health outcomes due to the inclusion of people who have given up drinking due to poor health in the non-drinker group ('sick-quitters').(40, 48) The detailed level of analysis in relation to these questions is beyond the scope of the present paper, and should be the subject of future investigation.

Interestingly, males were more likely to report tinnitus but females more likely to report tinnitus being bothersome. One explanation may be that because men are more likely to have hearing loss,(49) they are more likely to experience tinnitus. But men may be less likely

to report tinnitus as being bothersome due to differences in socialization that leads to men being less likely to acknowledge and report discomfort in relation to physical symptoms in general.(50)

Use of ototoxic medication was associated with prevalent tinnitus and bothersome tinnitus, but not with incidence tinnitus or changes in bothersomeness. The association between tinnitus and ototoxic medication is supported by other literature(51) as is the adverse effect on quality of life that results.(52) Though an association between smoking and tinnitus has been reported previously,(28, 53) there were no associations with tinnitus in the present analysis. Both metabolic syndrome and lack of physical activity have previously been associated with tinnitus (54) and tinnitus bothersomness,(55, 56) whilst physical activity was weakly associated with tinnitus in the current study. The relatively low baseline for being physically active (10 minutes daily moderate activity), and self report measure in the current study may help to explain this apparent anomaly. Previous studies utilising accelerometers have indicated that applying higher thresholds for physical activity produced more pronounced associations in older adult populations.(54)

Taken together, there is an indication that generally healthy lifestyle may be linked to reduced likelihood of tinnitus. Variations in findings relating to both factors across studies may relate to differences in measurement and the fact that both are also strongly associated with age, socioeconomic status, and sex. A limitation of the study is that the sample sizes were substantially lower for the longitudinal analyses; lack of longitudinal associations may be due to lack of statistical power. The analysis did not include potentially important explanatory factors (for example, personality factors besides neuroticism, leisure noise, and genetic factors) and some factors may not have been well captured by the measures available in this data set. For example, work- and music-related noise exposure was based on a self-report measure which corresponds to noise levels above 85 dB(A).(25) But the measure does not account for levels that may substantially exceed 85 dB(A) nor for the use or non-use of ear protection.

A key limitation of the present study – and all other tinnitus research - is the lack of a reliable measure of tinnitus, and no agreement about the validity or characterisation of

tinnitus phenotypes.(57) This point was highlighted in the present study: Of those originally reporting tinnitus with subsequent cessation at follow up, over one third now claimed never to have had tinnitus. This finding calls into question the reliability of the current self-report measures of tinnitus utilised in epidemiological research and suggests that a collaborative effort to arrive at a refined definition and appropriate measure of tinnitus should be made. There were no interactions between prevalent tinnitus, tinnitus bothersomeness or change in tinnitus bothersomeness with hearing aid use. These data suggest that poor hearing is the main driver of the risk of tinnitus, but that this is not offset by hearing aid use. Clinical experience, case series,(58) and retrospective studies(59) indicate that hearing aids can reduce or inhibit tinnitus, although to date no controlled trials have shown the benefits of hearing aids on tinnitus.(60) Given the modest and uncertain impact of hearing aids, public health approaches should focus on primary prevention of hearing loss in order to reduce the impacts of tinnitus. Additionally, given the largely persistent nature of tinnitus shown in the study, further attention should be paid to effectively managing symptoms in people with tinnitus, and ultimately to finding a cure.

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Author contributions

Piers Dawes; Writing, editing, statistical analysis

John Newall; Writing, editing

David Stockdale; Writing, editing

David M. Baguley; Writing, editing

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Reporting checklist for cross sectional study.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	7

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	7-10
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	9-10
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9-10
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9-10
Statistical methods	#12c	Explain how missing data were addressed	9-10
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10 & 12
Participants	#13b	Give reasons for non-participation at each stage	10-12
Participants	#13c	Consider use of a flow diagram	n/a

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	10 (table 2)
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	10
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	see tables 3-5
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
Main results	#16b	Report category boundaries when continuous variables were categorized	6-10
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	6-10
Discussion			
Key results	#18	Summarise key results with reference to study objectives	14-16
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	17
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

Notes:

- 14a: 10 (table 2)
- 15: see tables 3-5 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 02. June 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

The natural history of tinnitus in adults: a cross sectional and longitudinal analysis

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The natural history of tinnitus in adults: a cross sectional and longitudinal analysis

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Abstract

Objective

To assess incidence and changes in tinnitus and bothersome tinnitus as well as associated risk factors in a large sample of UK adults.

Design

Prospective cohort study

Setting

United Kingdom

Participants

For cross-sectional analysis, a group of 168,348 participants aged between 40 to 69 years with hearing and tinnitus data, from the UK Biobank resource. Longitudinal analysis included a subset of 4,746 people who attended a 4 year retest assessment.

Main outcome measures

Presence and bothersomeness of tinnitus.

Results

17.7% and 5.8% of participants reported tinnitus or bothersome tinnitus respectively. The 4 year incidence of tinnitus was 8.7%. Multivariate logistic regression models suggested that age, hearing difficulties, work noise exposure, ototoxic medication, and neuroticism were all positively associated with both tinnitus and bothersome tinnitus. Reduced odds of tinnitus, but not bothersome tinnitus was seen in alcohol drinkers versus non-drinkers. Male gender was associated with increased odds of tinnitus, whilst female gender was associated with increased odds of bothersome tinnitus. At follow up, of those originally reporting tinnitus, 18.3% reported no tinnitus. Of those still reporting tinnitus, 9% reported improvement, 9% reported tinnitus becoming more bothersome, with the rest unchanged. Male gender and alcohol consumption were associated with tinnitus being reported less bothersome, hearing difficulties were associated with the odds of tinnitus being reported as more bothersome.

Conclusions

This study is one of the few to provide data on the natural history of tinnitus in a non-clinical population, suggesting that resolution is relatively uncommon, with improvement and worsening of symptoms equally likely. There was limited evidence for any modifiable lifestyle factors being associated with changes in tinnitus symptoms. In view of the largely persistent nature of tinnitus, public health strategies should focus on i) primary prevention and ii) managing symptoms in people that have tinnitus, and monitoring changes in bothersomeness.

Keywords

Tinnitus, Biobank, natural history, incidence

Article Summary

Strengths and limitations of this study

- This study investigated both the prevalence and incidence of tinnitus and its correlates in a sample drawn from the UK Biobank resource.
- The study includes both a cross sectional analysis of a large sample (168,348 participants), with the longitudinal component based on a smaller sample (4,746 participants).
- The UK Biobank resource, from which the data was drawn, is not completely representative of the UK population.
- A wide range of relevant risk factors were available for the analysis.
- Lack of a consensus on the definition of tinnitus hampers comparison across the literature.

Introduction

Tinnitus (the subjective experience of sound perception when there is no external source) can be a troublesome experience, and when severe can be associated with insomnia, poor concentration, anxiety, and/or depression.(1) Around 10-15% of adults have tinnitus, and although cost effective, the cost of care of patients with tinnitus is high.(2) The question of the natural history of tinnitus in adults is of major importance for both patients and clinicians (3) but data regarding the natural history of tinnitus in adults are scant. A few studies have investigated tinnitus in various populations longitudinally (Table 1). Estimates of the incidence of tinnitus vary depending on the age of the population and the definition of tinnitus in each study. Such studies are useful in demand forecasting for diagnostic and therapy services, but do not support the counselling of existing tinnitus cases regarding their prognosis. The main limitation of many studies examining changes in tinnitus over time is that they were conducted with specific populations, clinical samples, or with people taking part in tinnitus research, and so may not be representative of the general population.

Clifford et al. (4) reported on the progression of tinnitus in a US Marine cohort, indicating that worsening tinnitus was associated with the presence of Post-Traumatic Stress Disorder, and moderate/severe Traumatic Brain Injury (TBI). One other study reported a modest improvement in the bothersomeness of tinnitus at follow up 4.9 years after treatment by a Clinical Psychologist, the majority (59%) having received cognitive behaviour therapy for tinnitus.(3) Another study reported that severity of symptoms tended to be more severe, with tinnitus of longer duration among patients presenting for tinnitus therapy.(5) A systematic review and meta-analysis reporting the experiences of patients with tinnitus who were research participants enrolled in control (waiting list) arms of clinical trials reported a small, statistically significant improvement in tinnitus symptoms over time, though clinical significance of these improvements was unclear.(6) Placebo groups in controlled clinical trials of tinnitus treatments have also reported reduced bothersomeness of tinnitus immediately and up to 14 weeks post placebo treatment.(7-9) In a conference report Smith and Coles(10) reported data regarding tinnitus from the UK National Study of Hearing.(11) Participants reporting tinnitus experiences were asked to retrospectively rate their tinnitus loudness and annoyance at two stages of their tinnitus experience: ‘onset to middle’ and ’middle/recent or end’. These ill-defined sample points render the data in this report are

hard to interpret, but it appears that in a small number (8.5%) the tinnitus had resolved completely, and that there was a general trend over time towards decreased annoyance.

Large scale data regarding longitudinal experiences of a general population regarding tinnitus has not been reported to date, with the closest examples examining samples an order of magnitude smaller than the present study.(12, 13) The only large scale population data available utilised indirect measures of tinnitus based on clinical record or health claim data. (14, 15) In the present study the aim was to establish the proportions of people who experience tinnitus and bothersome tinnitus, and changes in tinnitus and bothersome tinnitus over time and to determine demographic, health and lifestyle correlates, in order to inform patient counselling and identify potential avenues for prevention and treatment of tinnitus.

Table 1. Prevalence and/or incidence rates of tinnitus

Study	Definition of tinnitus	Population	Prevalence of tinnitus at baseline	Follow-up interval; Incident tinnitus;
Gopinath, McMahon (13)	Tinnitus over the past year lasting 5 minutes or longer	Australia Age: >=55 years Baseline (n=2006) Follow-up (n=1292, female=58.9%)	37% (481)*	**5 year follow-up;** Persisting: 82% (346) Resolved: 18% (78) Incidence: 18% (156)
Nondahl, Cruickshanks (12)	Tinnitus over the past year of i) at least moderate severity or causing difficulty with sleep ii) mild tinnitus not affecting sleep	United States Age: 48-92 years Baseline (n=3753, female=57.7%) Follow-up (n=2800, female=58.6%)	8.2% (moderate tinnitus) (308)	**5 year follow-up;** Incidence of significant tinnitus: 5.7% (143)
			20.2% (mild tinnitus) (754)	**5 year follow-up;** Persisting : 68.6% (394) Resolved : 31.4% (180)
Nondahl, Cruickshanks (16)	Tinnitus over the past year of at least moderate severity or causing difficulty with sleep	United States Age: 48-92 years Follow-up (n=2922, female:59.3%)	N.A.	**10 year follow-up;** 12.7% (371)

Lee, Do Han (14)	Based on record of health service utilisation for 'tinnitus' through the Korean National Health Insurance Service	South Korea Age: all ages Follow-up (n=51 million, female= not reported)	12.58-14.62 per 1000 from 2006-2015	**Yearly incidence;** 8.26-9.49 per 1000 from 2006-2015 9.1% 10 year incidence
Martinez, Wallenhorst (15)	Any tinnitus: based on health service utilisation for 'tinnitus' gathered through the United Kingdom Clinical Practice Research Datalink Significant tinnitus: as above but with related follow up within 28 days. See Martinez for full definition (15)	United Kingdom Age: <=85 years Follow-up (n=4.7 million, female= 50.5%)	N.A.	**10 year follow-up;** Incidence significant tinnitus 5.4 per 10,000 person years Incidence any tinnitus 47.3 per 10,000 person years

Methods

Participants

Participants were drawn from the UK Biobank, an international resource for studying the genetic, environmental and lifestyle causes of diseases of middle and older age.(17) Participant recruitment was conducted via the UK National Health Service and aimed to be as inclusive as possible of the UK population. In total, 9.2 million invitations were sent to recruit 503,325 participants who were aged between 40 to 69 years between 2006 to 2010, a response rate of 5.47%. The UK Biobank sample contains a higher proportion of females, people reporting White British ethnic background and people living in less deprived areas than the general population.(18) The UK Biobank sample is not representative of the UK general population, but the disease-exposure relationships are thought to generalizable due to the size and inclusiveness of the sample. Hearing and tinnitus measures were included part way through data collection, so information on tinnitus at baseline was available for 168,348 participants.

Participants attended an assessment centre where data on demographic, health, environmental and lifestyle factors were collected via computerised questionnaire along with physical measures including hearing testing during assessments of around 90 minutes in duration. Further information on procedures and the data collected is contained on the

UK Biobank website (http://www.ukbiobank.ac.uk/). During 2012 and 2013, 17,819 participants attended a retest assessment, with a 21% response rate. All baseline measures were repeated, including hearing and tinnitus. The mean retest interval was 4.3 years (range 2 to 7 years); retest tinnitus data were available for 4,746 participants. (For further details of the repeat assessment, see http://biobank.ctsu.ox.ac.uk/~bbdatan/Repeat_assessment_doc_v1.0.pdf). UK Biobank received ethical approval from the North West-Haydock National Research Ethics Committee (Ref 11/NW/0382), and all participants provided written informed consent.

Information on sex and ethnicity (based on 2001 UK Census categories) and area of residence was collected. Area of residence was used to determine a Townsend deprivation score. The Townsend deprivation score is a proxy for socioeconomic status, and is applicable across the countries of the UK.(19) Townsend scores are based on four variables; unemployment, non-car ownership, non-home ownership and household overcrowding. Each variable is normalised relative to national levels and summed to provide an overall deprivation index. Higher scores represent more deprived (less affluent) socioeconomic status. A score of 0 represents the national mean with a standard deviation of 1. Townsend scores for areas of residence ranged between 14.01 and -5.59 in the 2011 census.(20) In the regression analyses below, Townsend scores were grouped from least to most deprived quartiles in the study sample.

Tinnitus

Participants were asked "Do you get or have you had noises (such as ringing or buzzing) in your head, or in one or both ears, that lasts for more than five minutes at a time?". In this analysis, tinnitus was identified based on responses of ‘yes most of the time’, ‘yes a lot of the time’ or ‘yes some of the time’, similar to criteria used in other studies of the epidemiology of tinnitus (21-23). If a participant reported that they did experience tinnitus that lasted for more than five minutes at a time, they were asked "How much do these noises worry, annoy or upset you when they are at their worst?"; severely, moderately, slightly or not at all. In this analysis, ‘bothersome’ tinnitus was identified on the basis of responses of either ‘moderately’ or ‘severely’.

Incident tinnitus was identified if a person who did not report tinnitus at baseline reported tinnitus at least some of the time at retest. Among those who reported tinnitus at baseline, 'Worse tinnitus' was identified if someone reported their tinnitus as not being bothersome at baseline (i.e. 'slightly' or 'not at all') but reported their tinnitus being bothersome at follow up (i.e. 'moderately' or 'severely').

Hearing

Participants completed an English version of the Digit Triplet Test (DTT), a test of speech recognition in noise developed for large scale hearing screening.(24, 25) The DTT correlates strongly with audiometric thresholds. The DDT is described elsewhere (http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100049). In short, fifteen sets of three monosyllabic digits (e.g. 6-1-3) were presented over circumaural headphones with the volume of presentation set to a comfortable level. Digits were presented in background noise shaped to match the spectrum of the spoken digits. Noise levels varied adaptively to track a SNR for the 50% speech recognition threshold (SRT), which was based on the mean SNR for the last eight triplets. Lower (more negative scores) indicate better performance. Hearing was additionally indexed by self-reported hearing status with the question "Do you have any difficulty with your hearing?".

Occupation- and music-related noise exposure, ototoxic medication, metabolic syndrome, physical activity, smoking, alcohol consumption and hearing aid use

The potential associations between tinnitus and risk factors were explored using a previously identified list and discussion between the authors.(1) Occupational and music-related noise exposure was identified on the basis of any reported exposure in response to the questions "*Have you ever worked in a noisy place where you had to shout to be heard?*" and "*Have you ever listened to music for more than 3 hours per week at a volume which you would need to shout to be heard or, if wearing headphones, someone else would need to shout for you to hear them?*". The criterion for work- and music-related noise corresponds to exposure estimated to exceed 85 dB(A) (26). Use of ototoxic medication was identified on the basis of reported regular (daily, weekly or monthly) use of medications known to have ototoxic properties (including loop diuretics, aminoglycoside antibiotics, quinine derivatives, non-steroidal anti-inflammatories and salicylates). Metabolic syndrome was identified based

on the Adult Treatment Panel III report of the National Cholesterol Education Program (ATP III NCEP) criteria;(27) positive risk was identified on the basis of three or more of waist circumference of ≥102 cm in men and ≥88 cm in women; participant report of high cholesterol or if the participant reported they were currently taking medication for high cholesterol; measured systolic blood pressure greater than 130 mm Hg or diastolic pressure greater than 85 mm Hg; participant report of diabetes or the use of medication for diabetes. Participants were identified as being physically 'active' if they reported doing more than 10 minutes of physical activity in relation to the question "Yesterday, about how long did you spend doing activities that needed moderate effort, making you somewhat short of breath? For example walking upstairs, going to the gym, jogging, energetic dancing, aerobics, most sports, using heavy power tools and other physically demanding DIY & gardening." 'Inactive' participant were identified on the basis of physical activity of 10 minutes or less. Current or previous tobacco smoking was identified on the basis of positive responses to two questions; "Do you smoke tobacco now?" and "In the past, how often have you smoked tobacco?" Alcohol drinkers were identified on the basis of any report of current alcohol consumption ("About how often do you drink alcohol?"; 'Special occasions only', 'One to three times a month', 'One or twice a week', 'Three or four times a week' or 'Daily or almost daily'). Non-drinkers were categorised based on a response of 'Never'. Hearing aid use was identified on the basis of a 'yes' response to "Do you use a hearing aid most of the time?".

Neuroticism

Neuroticism scores were based on summed positive responses to 12 items from the Eysenck Personality Questionnaire Revised(EPQ-R),(28) including Does your mood often go up and down?; Do you ever feel 'just miserable' for no reason?; Are you an irritable person?; Are your feelings easily hurt?; Do you often feel 'fed-up'?; Would you call yourself a nervous person?; Are you a worrier?; Would you call yourself tense or 'highly strung'?; Do you worry too long after an embarrassing experience?; Do you suffer from 'nerves'?; Do you often feel lonely?; Are you often troubled by feelings of guilt?. Scores are summed to provide an integer score between 1 and 12 representing the number of neurotic traits present, with higher scores indicating greater neuroticism.

Data Analysis

Cross tabulations performed to describe characteristics of those who reported tinnitus versus no tinnitus, and the subset of people with tinnitus who reported 'bothersome' tinnitus. Demographic, health, lifestyle and psychological characteristics were selected on the basis of previously being linked to tinnitus.(22, 29, 30) There were missing data for some measures primarily due to measures being added to the study protocol at different time points during data collection (see Table 2). Because the reason for the missing data was not systematically related to the outcomes of interest in this study, it was assumed that the data were missing completely at random. Missing variable analysis did not identify any pattern to the missing data. Multinomial logistic regression was used to model cross-sectional baseline associations between demographic, hearing, noise exposure, health and lifestyle factors and tinnitus (versus no tinnitus) and bothersome tinnitus (versus non-bothersome tinnitus). A Cox proportional hazard model was used to model the incidence of tinnitus and more bothersome tinnitus at 4 year follow-up. All the statistical assumptions for performing the Cox proportional hazard model were met. Analyses were performed with IBM SPSS version 23.(31)

Patient and public involvement

Patient and public involvement is reported according to the Guidance for Reporting Involvement of Patients and the Public (GRIPP) – short form 17. 1. Aim: UK Biobank consulted with stakeholders including the public at several times during the planning stages and post implementation to obtain guidance and feedback in relation to; consent, confidentiality, access, commercialisation, and oversight/monitoring. The conception of the project and its aim sprung directly from public enquiries fielded by the British Tinnitus Association a partner in this project. 2. Methods: For the UK Biobank, a key element in the public consultation process was an initial workshop which included 20 members of the public in the study target age range and 10 outside the target age range. Sessions key points were noted, and sessions tape recorded, a post workshop questionnaire was sent to all attendees, and to any stakeholders who were not able to attend the workshops in person (to increase representativeness). 3. Results: Public opinion across many areas addressed in the aims was diverse, a full report can be found at http://www.ukbiobank.ac.uk/public-consultation/ 4. Discussion: Public input influenced ethical considerations, access to data, the consent process, the commercialisation of the resource, and oversight/monitoring. 5.

Reflections/critical perspective: Public and other stakeholder input into the study was essential to ensure public confidence in the study conduct, and to respond to public concerns with the resource. Whilst efforts were taken to consider public input, the diversity of opinion meant that not all perspectives were equally influential on the UK Biobank's design and conduct.

Results

Cross-sectional analysis

In this sample of adults aged 40 to 69 years, 17.7% (n = 29,861) reported tinnitus and 5.8% (n = 9,751) reported bothersome tinnitus. Table 2 summarises the characteristics of participants who reported that they experienced tinnitus versus those who did not report tinnitus. Characteristics of those who reported tinnitus are broken down further with respect to whether participants reported their tinnitus as being bothersome or not bothersome.

Table 2. Sample characteristics

	No tinnitus	Tinnitus		
		Any tinnitus (Not bothersome + Bothersome)	Not bothersome	Bothersome
	N = 138,487	N = 29,861	N = 20,110	N = 9,751
Age (168,348)*	56.4 (SD 8.2)	58.7 (SD 7.58)	57.5 (SD 8.22)	58.0 (SD 7.78)
Sex (male; 168,348)	44.0%	52.80%	51.0%	45.70%
Social economic status score+ (168,079)	-1.12 (SD 2.92)	-0.99 (SD 3.01)	-1.02 (SD 3.00)	-0.66 (SD 3.16)
SRT better ear (157,574)	-7.43 (SD 1.62)	-7.07 (SD 1.96)	-7.26 (SD 1.80)	-6.91 (SD 2.13)
Hearing difficulties (168,348)	21.3%	56.4%	43.4%	63.3%
Work noise exposure (166,805)	20.5%	34.4%	32.2%	37.0%
Music noise exposure (165,977)	11.5%	16.6%	17.4%	18.5%
Physical activity (106,989)	71.1%	71.7%	71.5%	69.3%
Ototoxic medication (168,348)	39.2%	46.5%	44.6%	53.1%
Alcohol drinker (168,201)	91.5%	90.1%	91.2%	88.1%
Current or previous smoking (167,725)	43.9%	48.5%	47.4%	50.7%
Metabolic risk (168,348)	9.1%	12.0%	10.7%	13.3%
Neuroticism score (136,600)	3.98 (SD 3.22)	4.63 (SD 3.41)	4.44 (SD 3.33)	5.64 (SD 3.47)

*The number in brackets indicates the number of participants that completed each measure.
+Social economic status indexed by Townsend deprivation index score; lower (more negative) score indicate less deprived (more affluent) status

All variables were entered simultaneously into multi-variable logistic regression model for tinnitus versus no tinnitus (of the original sample of 168,348, after excluding all participant with missing data 80,380 participants were included in the analysis). A multi-variable logistic regression model was also conducted to compare bothersome tinnitus versus not bothersome tinnitus (of the original sample of 29,861 tinnitus sufferers after excluding all participants with missing data, 21,690 were included in the analysis)(Table 3). Similar patterns of association were observed for tinnitus and bothersome tinnitus. The Nagelkerke r^2 was 0.143 for tinnitus and 0.067 for bothersome tinnitus. Older age, male sex, poorer speech recognition threshold, hearing difficulties, work noise exposure, music noise exposure, physical activity, regular use of ototoxic medication, and neuroticism were associated with tinnitus. Alcohol consumption was associated with lower odds of tinnitus. Female sex, most deprived social economic status, poorer speech recognition threshold, hearing difficulties, work noise exposure, ototoxic medication and neuroticism were associated with bothersome tinnitus. The sample included 1013 hearing aid users. The analyses were re-run to check for interactions with hearing difficulties and hearing aid use on tinnitus and bothersome tinnitus. There was no significant hearing aid by hearing difficulties interaction for tinnitus (OR 0.50 95% confidence interval 0.21 – 1.21, $p = 0.125$) or bothersome tinnitus (OR 0.87 95% confidence interval 0.18 – 4.18, $p = 0.888$).

Table 3. Cross-sectional correlates of tinnitus and bothersome tinnitus

	Tinnitus N=80,380 $\chi^2(15) = 7110.23$, $p < 0.001$				Bothersome tinnitus N=21,690 $\chi^2(15) = 912.89$, $p < 0.001$			
		95% C.I. for EXP(B)				95% C.I. for EXP(B)		
	Exp(B)	Lower	Upper	p	Exp(B)	Lower	Upper	p
Age	**1.03**	**1.03**	**1.03**	**0.000**	1.00	1.00	1.01	0.176
Sex (male)	**1.20**	**1.15**	**1.25**	**0.000**	**0.74**	**0.68**	**0.80**	**0.000**
Social economic status				0.294				0.023
First Quartile 1 (Reference)				-				-
Second Quartile	1.02	0.97	1.08	0.484	0.95	0.86	1.05	0.297
Third Quartile	0.98	0.93	1.04	0.480	1.03	0.93	1.14	0.587
Fourth Quartile (most deprived)	1.03	0.98	1.09	0.262	**1.11**	**1.00**	**1.23**	**0.043**

SRT better ear	**1.03**	**1.02**	**1.04**	**0.000**	**1.02**	**1.00**	**1.05**	**0.020**
Hearing difficulties (yes)	**3.75**	**3.60**	**3.90**	**0.000**	**2.07**	**1.92**	**2.23**	**0.000**
Work noise exposure (yes)	**1.40**	**1.34**	**1.47**	**0.000**	**1.15**	**1.06**	**1.25**	**0.001**
Music noise exposure (yes)	**1.39**	**1.31**	**1.47**	**0.000**	1.03	0.93	1.13	0.576
Physical activity (yes)	**1.05**	**1.00**	**1.09**	**0.038**	0.97	0.89	1.04	0.372
Ototoxic medication (yes)	**1.18**	**1.13**	**1.23**	**0.000**	**1.19**	**1.11**	**1.28**	**0.000**
Alcohol drinker (yes)	**0.87**	**0.80**	**0.93**	**0.000**	0.89	0.78	1.01	0.070
Current or previous smoking (yes)	0.99	0.95	1.03	0.500	1.04	0.97	1.12	0.300
Metabolic risk (yes)	1.05	0.98	1.12	0.210	0.97	0.86	1.09	0.601
Neuroticism score	**1.05**	**1.04**	**1.06**	**0.000**	**1.10**	**1.08**	**1.11**	**0.000**

Longitudinal analysis

A subset of participants (3997 people) who had completed the questions about tinnitus and the full set of correlates of interest were included in the longitudinal analysis, with a mean retest interval of 4.3 years (2-7 years range). There were 276 cases of incident tinnitus among the 3,177 people who did not report tinnitus at baseline; a 4 year incidence of 8.7%. The Cox proportional hazard model for incident tinnitus between baseline and 4 year follow-up was not statistically significant ($\chi^2(15) = 21.6$, $p = 0.119$). Among the 820 people who reported tinnitus at baseline and completed responses at follow-up, 150 reported no tinnitus at follow-up (including 63 who claimed never to have had tinnitus); 18.3% of people reporting tinnitus at baseline did not report tinnitus at follow-up. Of the 820 tinnitus sufferers completing follow up, after excluding cases of missing data 565 were included in the Cox proportional hazard model. The analysis suggests that only hearing difficulties were associated with reduced likelihood of no tinnitus at follow-up(Table 4).

Table 4. Cox proportional hazard model for no tinnitus at follow-up (i.e. resolved tinnitus)

	Resolved tinnitus

	N=565 ($\chi^2(15) = 26.7$, $p = 0.031$)			
		95% confidence interval		
	β	Lower	Upper	*p*
Age	0.99	0.96	1.03	0.683
Sex (male)	0.96	0.62	1.47	0.841
Social economic status				0.558
First Quartile 1 (Reference)				-
Second Quartile	1.11	0.69	1.80	0.671
Third Quartile	0.72	0.39	1.30	0.273
Fourth Quartile (most deprived)	1.01	0.55	1.85	0.972
SRT better ear	0.98	0.88	1.10	0.735
Hearing difficulties (yes)	**0.48**	**0.32**	**0.74**	**0.001**
Work noise exposure (yes)	1.47	0.95	2.26	0.080
Music noise exposure (yes)	1.26	0.76	2.09	0.379
Physical activity (yes)	1.48	0.84	2.58	0.173
Ototoxic medication (yes)	0.83	0.55	1.25	0.383
Alcohol drinker (yes)	0.66	0.30	1.47	0.309
Current or previous smoking (yes)	1.19	0.79	1.78	0.399
Metabolic risk (yes)	0.66	0.35	1.25	0.203
Neuroticism score	1.05	0.99	1.12	0.101

Among the 1,039 people who completed questions about tinnitus annoyance at baseline and follow-up, 850 (81.8%) reported no change, 93 (9%) reported that their tinnitus was more bothersome and 93 (9%) reported their tinnitus being less bothersome.

In a Cox proportional hazard model, of those who completed follow up and who reported "not at all" or "slightly" bothersome tinnitus at baseline cases of tinnitus being reported as being more bothersome (versus those reporting no change) were associated with higher (poorer) better ear SRT, non-drinking and female gender (Table 5). The sample included 27 hearing aid users, and the model was re-run to check for an interaction with hearing aid use and speech reception threshold. The interaction was not statistically significant (OR 0.88, 95% confidence interval 0.67 – 1.14, $p = 0.337$). The model for reduced bothersomeness was not statistically significant $\chi^2(15) = 24.1$, $p = 0.063$.

Table 5. Cox proportional hazard model for tinnitus bothersomeness worse

	Bothersomeness worse N=404 $\chi^2(15) = 34.4$, $p = 0.003$

		95% confidence interval		
	β	Lower	Upper	*p*
Age	0.98	0.93	1.04	0.481
Sex (male)	**0.44**	**0.22**	**0.86**	**0.017**
Social economic status				0.258
First Quartile 1 (Reference)				-
Second Quartile	1.66	0.80	3.48	0.176
Third Quartile	0.77	0.27	2.23	0.633
Fourth Quartile (most deprived)	0.77	0.27	2.19	0.621
SRT better ear	**1.13**	**1.02**	**1.27**	**0.026**
Hearing difficulties (yes)	2.01	0.96	4.20	0.063
Work noise exposure (yes)	1.41	0.71	2.83	0.329
Music noise exposure (yes)	1.15	0.50	2.63	0.738
Physical activity (yes)	0.88	0.39	1.96	0.752
Ototoxic medication (yes)	1.24	0.65	2.34	0.513
Alcohol drinker (yes)	**0.30**	**0.11**	**0.87**	**0.026**
Current or previous smoking (yes)	1.61	0.83	3.11	0.156
Metabolic risk (yes)	0.67	0.22	2.04	0.485
Neuroticism score	0.95	0.86	1.06	0.381

Discussion

In cross-sectional analysis, 17.7% of adults 40-69 years old reported tinnitus, with 5.8% reporting that tinnitus was bothersome. The 4 year incidence of tinnitus in this sample was 8.7%. The study offered some cause for optimism with respect to the natural history of tinnitus; around 18% of people who reported tinnitus at baseline did not report tinnitus at follow-up, an average of 4 years later. For those that continued to experience tinnitus, 81.8% reported that tinnitus bothersomeness was unchanged after 4 years, 9% reported tinnitus became worse (previously not bothersome, now bothersome), and in 9% better (previously bothersome, now not). The strengths of the study include the large inclusive sample, which was not derived from a specific tinnitus nor hearing study. The availability of longitudinal data was a significant strength. Longitudinal tinnitus data are available in a very small number of other studies. The use of standard tinnitus phenotype questions allowed comparison of these results with those of other studies. Although accounted for in the model, the variability in time elapsed at retest (2-7 years) may be a limitation. However the minimum of 2 years is longer than the period of most intervention studies and provides time

to observe natural variation in tinnitus. In terms of patient counselling about long term prognoses for tinnitus, the 4 year mean follow up period limits the certainty of any opinion in relation to longer-term outcomes. One significant limitation of the study is the possibility that a person may have received clinical help for tinnitus during the intervening years. Most people seek help within the first year of onset,(32) so this is unlikely to have been the case for a large proportion of participants here. Unfortunately, information about receiving clinical help and the duration of tinnitus was not available in this study and this limits our confidence in stating that all cases of spontaneous recovery, were indeed spontaneous.

Tinnitus correlates

Poorer hearing (better ear SRT and self-reported hearing difficulties) was associated with the presence of tinnitus and bothersome tinnitus. Hearing difficulties were associated with lower likelihood of resolved tinnitus and SRT with lower likelihood of tinnitus being less bothersome over time. But there was no relationship between SRT or hearing difficulties and incident tinnitus. A relationship between tinnitus and hearing loss is consistently reported (22, 33-36) with hearing loss being proposed as a trigger for tinnitus which then persists due to maladaptive plasticity in the central auditory and associated systems.(37) The lack of a relationship between hearing and incident tinnitus may be due to the much smaller sample for the longitudinal analysis versus the cross-sectional analysis. Work noise exposure was associated with prevalent tinnitus and bothersome tinnitus. Music exposure was associated with prevalent tinnitus. Noise exposure is the primary modifiable risk factor for tinnitus (34, 38, 39) and the pathophysiological impact can be either cochlear hair cell dysfunction, leading to a subjective hearing loss, and/or cochlear synaptopathy, the effects of which are more subtle.(40)

Alcohol consumption was associated with reduced odds of tinnitus, but not of bothersome tinnitus. Moderate alcohol consumption has been suggested to have a protective effect on hearing, perhaps via cardiovascular pathways.(41, 42) Other studies reported no association between alcohol consumption and tinnitus,(43, 44) with one study reporting increased risk of tinnitus with alcohol consumption.(42) There are several difficulties with disentangling the effect of alcohol consumption on tinnitus. First, alcohol consumption is highly confounded with socio-cultural factors that may also impact on health, including

hearing.(45) Second, impacts of alcohol consumption may be dose-dependent; heavy alcohol consumption is certainly bad for general health, including hearing.(46) Impacts may be different for moderate or light levels of consumption.(46-48) Third, comparing health outcomes in drinkers versus non-drinkers may give the false impression that alcohol consumptions is linked to better health outcomes due to the inclusion of people who have given up drinking due to poor health in the non-drinker group ('sick-quitters').(41, 49) The detailed level of analysis in relation to these questions is beyond the scope of the present paper, and should be the subject of future investigation.

Interestingly, males were more likely to report tinnitus but females more likely to report tinnitus being bothersome. One explanation may be that because men are more likely to have hearing loss,(50) they are more likely to experience tinnitus. But men may be less likely to report tinnitus as being bothersome due to differences in socialization that leads to men being less likely to acknowledge and report discomfort in relation to physical symptoms in general.(51) Higher neuroticism scores were also associated with increased odds of both tinnitus and bothersome tinnitus, in line with previous research. (52) The lack of association between neuroticism and increased bothersomeness of tinnitus over time suggests that neuroticism and psychological discomfort may be a consequence of, rather than a risk for bothersome tinnitus.

Use of ototoxic medication was associated with prevalent tinnitus and bothersome tinnitus, but not with incidence of tinnitus or changes in bothersomeness. The association between tinnitus and ototoxic medication is supported by other literature (53) as is the adverse effect on quality of life that results.(54) Though an association between smoking and tinnitus has been reported previously,(29, 55) there were no associations with tinnitus in the present analysis. Both metabolic syndrome and lack of physical activity have previously been associated with tinnitus (56) and tinnitus bothersomeness,(57, 58) whilst physical activity was weakly associated with tinnitus in the current study. The relatively low baseline for being physically active (10 minutes daily moderate activity), and self report measure in the current study may help to explain this apparent anomaly. Previous studies utilising accelerometers have indicated that applying higher thresholds for physical activity produced more pronounced associations in older adult populations.(56)

Taken together, there is an indication that generally healthy lifestyle may be linked to reduced likelihood of tinnitus. Variations in findings relating to both factors across studies may relate to differences in measurement and the fact that both are also strongly associated with age, socioeconomic status, and sex. A limitation of the study is that the sample sizes were substantially lower for the longitudinal analyses; lack of longitudinal associations may be due to lack of statistical power. The analysis did not include potentially important explanatory factors (for example, personality factors besides neuroticism, leisure noise, and genetic factors) and some factors may not have been well captured by the measures available in this data set. For example, work- and music-related noise exposure was based on a self-report measure which is estimated to correspond to noise levels above 85 dB(A).(26) But the measure does not account for levels that may substantially exceed 85 dB(A) nor for the use or non-use of ear protection.

A key limitation of the present study – and all other tinnitus research - is the lack of a reliable objective measure of tinnitus, and no agreement about the validity or characterisation of tinnitus phenotypes.(59) This point was highlighted in the present study: of those originally reporting tinnitus with subsequent cessation at follow up, over one third now claimed never to have had tinnitus. This finding calls into question the reliability of the current self-report measures of tinnitus utilised in epidemiological research and suggests that a collaborative effort to arrive at a refined definition and appropriate measure of tinnitus should be made.

There were no interactions between prevalent tinnitus, tinnitus bothersomeness or change in tinnitus bothersomeness with hearing aid use. These data suggest that poor hearing is the main driver of the risk of tinnitus, but that this is not offset by hearing aid use. Clinical experience, case series,(60) and retrospective studies(61) indicate that hearing aids can reduce or inhibit tinnitus, although to date no controlled trials have shown the benefits of hearing aids on tinnitus.(62) The UK Biobank data did not include information on other tinnitus therapies, used either individually, or in combination with hearing aids, some of which have shown promising results. (63) Given the modest and uncertain impact of hearing aids, public health approaches should focus on primary prevention of hearing loss in order to reduce the impacts of tinnitus. Additionally, given the largely persistent nature of tinnitus

shown in the study, further attention should be paid to effectively managing symptoms in people with tinnitus, and ultimately to finding a cure.

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Author contributions

Piers Dawes; Writing, editing, statistical analysis

John Newall; Writing, editing

David Stockdale; Writing, editing

David M. Baguley; Writing, editing

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