Understanding Factors That Cause Tinnitus: A Mendelian Randomization Study In The UK Biobank

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Abstract

Objectives: To investigate the causal role of established risk factors and associated conditions to tinnitus and tinnitus severity in UK Biobank. Design: Prospective cohort study with large dataset of >500,000 individuals. Analytical sample of 129,731 individuals in UK Biobank, of European descent. Participants were recruited from National Health Service registries, baseline age range between 37-73 years, response rate to baseline survey 6%. Participants were asked subjective questions about tinnitus and its severity. Previously observed associations (n=23) were confirmed in the UK Biobank using logistic and ordinal regression models. 2-sample Mendelian randomisation approaches were then used to test causal relationships between the 23 predictors and tinnitus and tinnitus severity. The main outcome measures were observational and genetic association between key demographics and determinants and two tinnitus outcomes (current tinnitus and tinnitus severity). Results: Prevalence of tinnitus was 20% and severe tinnitus 3.8%. The observational results are consistent with the previous literature, with hearing loss, older age, male gender, high BMI, higher deprivation, higher blood pressure, smoking history as well as numerous comorbidities being associated with higher odds of current tinnitus. Mendelian randomisation results showed causal correlations with tinnitus. Current tinnitus was predicted by genetically instrumented hearing loss (OR: 8.65 [95% CI: 6.12 to 12.23]), major depression (OR: 1.26 [95% CI: 1.06 to 1.50]), neuroticism (OR: 1.48 [95% CI: 1.28 to 1.71]) and higher systolic blood pressure (OR: 1.01 [95% CI: 1.00 to 1.02]). Lower odds of tinnitus were associated with longer duration in education (OR: 0.74 [95% CI: 0.63 to 0.88]), higher caffeine intake (OR:0.89 [95% CI: 0.83 to 0.95]) and being a morning person (OR: 0.94 [95% CI: 0.90 to 0.98]). Tinnitus severity was predicted by a higher genetic liability to neuroticism (OR:1.15 [95% CI: 1.06 to 1.26]) and schizophrenia (OR: 1.02 [95% CI:
Conclusions: Tinnitus data from the UK Biobank confirms established associated factors in the literature. Genetic analysis determined causal relationships with several factors that expand the understanding of the aetiology of tinnitus and can direct future pathways of clinical care and research.

INTRODUCTION

Tinnitus is described as “the conscious perception of an auditory sensation in the absence of a corresponding external stimulus” (Baguley et al., 2013). Estimates of global prevalence of tinnitus in adults range between 5.1 and 42.7% (McCormack et al., 2016). Whilst tinnitus for most sufferers is a mild annoyance only, bothersome tinnitus has been reported in 3-30.9% of the population (Coles, 2011; McCormack et al., 2016). Approximately 20% of patients with tinnitus seek medical intervention (Tang et al., 2019). Tinnitus represents a significant burden to healthcare systems across the world, with an estimated National Health Service (NHS) healthcare bill in the UK of £750 million (Stockdale et al., 2017). Tinnitus can affect a person’s quality of life and lead to social isolation, stress and lack of self-control (Baigi et al., 2011; Welch & Dawes, 2008), difficulty sleeping and psychological disturbances (Langenbach et al., 2005), along with an overall negative perception of general health and quality of life (Lasisi et al., 2010; Negrila-Mezei et al., 2011). Certain psychological and personality characteristics are hypothesised to be predisposing factors to developing tinnitus. Neuroticism, the tendency to experience negative and distressing emotions, has shown to be associated with the experience of tinnitus and its severity (Langguth et al., 2007; McCormack, Edmondson-Jones, Fortnum, et al., 2014). This suggests that
there is a complex interaction between mental health and tinnitus in which the tinnitus sufferer can be predisposed to experience more severe tinnitus by certain personality traits and conversely, the experience of tinnitus itself can cause significant emotional and psychological distress (Bhatt et al., 2017; Kim HJ, 2015; Krog et al., 2010; L et al., 1991; Langenbach et al., 2005; Nondahl et al., 2011).

The aetiology and pathophysiology of tinnitus are poorly understood (McFerran, 2018). It has been suggested that tinnitus is a systemic problem resulting from an imbalance in the excitatory and inhibitory inputs to auditory neurons (Kaltenbach, 2011), but it can arise from dysfunction or pathology at various sites of the hearing pathway from the cochlea to the auditory nerve and the central auditory system (Jastreboff, 1999) Tinnitus has been shown to correlate with increasing age and hearing impairment (Baguley et al., 2013; Dawes et al., 2014; Martinez et al., 2015; McCormack, Edmondson-Jones, Fortnum, et al., 2014). Many other factors have been implicated in the literature such as certain anthropometric factors, education, behavioural traits, cardiovascular and metabolic markers as well as several underlying conditions (Table 1). However, the evidence for many of these factors is inconclusive, for example findings for the role of gender, alcohol intake and smoking on tinnitus demonstrate conflicting results in different studies (Bhatt et al., 2016; McCormack, Edmondson-Jones, Fortnum, et al., 2014; Nondahl et al., 2011; Nondahl et al., 2002; St. Claire et al., 2010; Stohler et al., 2019). For example, some studies have shown tinnitus to be more prevalent in males whilst others in females (Bhatt et al., 2017; Nondahl et al., 2011; Nondahl et al., 2002). This may be a result of the datasets used, with observational studies providing the current evidence. These observational studies should be interpreted with caution, as it is very difficult to ascertain causality within
observational settings, as the findings can be subject to confounding or reverse causation. Mendelian Randomisation (MR; Figure 1) is a genetic technique use to infer causal pathways between an exposure and an outcome by using the genetic variants associated with the exposure of interest. This method can help us to determine if causal pathways exist between a range of predictors and tinnitus. The variants associated with the exposure (e.g. alcohol consumption) can be used as an unconfounded proxy for the exposure because their inheritance is random. This method is now extensively used to infer causal pathways.

Here, we have utilised the UK Biobank to test for causal relationships between the predictors and tinnitus using MR methods. The UK Biobank has extensive phenotypic and genetic data available on over 500,000 participants. Within this study, we have used data from 26,264 participants reporting tinnitus and 103,467 participants who did not report tinnitus. We performed observational associations between the predictors listed in Table 1 and tinnitus. We then tested for evidence of a causal relationship between the predictors and the current tinnitus using MR; and tested whether any predictors caused more severe tinnitus.

MATERIALS AND METHODS

UK Biobank
The UK Biobank resource is a study of just over 500,000 recruited from across the UK between 2006 and 2010. Participants were aged between 37 and 73 at recruitment (with >99.5% aged between 40 and 70). Extensive data were collected on all participants and they agreed to have their health followed over time, as previously comprehensively described (Bycroft et al., 2018; Collins, 2012). Genetic data were available for all individuals, with SNP genotypes generated from the Affymetrix Axiom UK Biobank array (~450,000 individuals) and the UKBiLEVE array (~50,000). This dataset underwent extensive central quality control (Bycroft et al., 2018).

In this study we used a subset of 129,731 individuals aged between 40 and 71 at recruitment in the UK Biobank who had tinnitus data available and were defined as of European descent using genetic analyses as previously described. Briefly, Principal Component Analyses (PCA) was performed to generate principal components using loadings from high-confidence Single Nucleotide Polymorphisms (SNPs) in the 1000 Genomes Cohort. The loadings were then used to project all of the UK Biobank samples into the same principal component space, and individuals were then clustered using the first four principal components.

A subset of unrelated individuals (n=110,767) was also defined, using the KING Kinship matrix to separate out related individuals (up to third degree). Ancestral principal components were generated within these individuals to allow us to account for subtle genetic differences at the population level.

Public And Patient Involvement
The details of patient and public involvement in the UK Biobank are available online (www.ukbiobank.ac.uk/about-biobank-uk/ and https://www.ukbiobank.ac.uk/wp-content/uploads/2011/07/Summary-EGF-consultation.pdf?phpMyAdmin=trmKQlYdijnQlgJ%2CfAzikMhEnx6). Here, there was no specific patient involvement in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of this study. No patients were asked to advise on interpretation or writing up of results. The UK Biobank will disseminate key findings from projects on its website.

Ethics Approval

In UK Biobank, ethical approval for data collection was received from the North-West Multi-centre Research Ethics Committee and the research was carried out in accordance with the Declaration of Helsinki of the World Medical Association. Participants in UK Biobank gave informed consent. No additional ethical approval was required for the analyses of the data. We applied for the data from UK Biobank and were approved (project number: 19819).

Exposure And Outcome Measures

- Exposures

Potential exposures were considered if there was a) prior evidence in the scientific literature of an association with tinnitus and b) known genetic variants associated with the exposure for use in Mendelian randomisation (see Genetic Analysis section). A full list of the exposures considered in this study is available
in Table 1 and more information about the derivation of these exposure variables in UK Biobank is provided in the Supplementary Table 2.

- **Tinnitus And Tinnitus Severity**

  Information about the presence of tinnitus was derived in UK Biobank based on responses to the question: “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?” with the option to select “yes, now most or all of the time”, “yes, now a lot of the time”, “yes, now some of the time”, “yes, not now but have had in the past”, “no, never”, “do not know” and “prefer not to answer”. This variable was utilised to derive current tinnitus (all positive responses except “yes, not now but have had in the past”) were coded as cases and those responding “no, never” as controls (N related cases=26,264; N related controls=103,467; N unrelated cases=22,293; N unrelated controls=88,474). All individuals reporting ever tinnitus (all positive responses to the above question) were subsequently asked “How much do these noises worry, annoy or upset you when they are at their worst?” Participants were able to select “severely”, “moderately”, “slightly”, “not at all”, “do not know” and “prefer not to answer”. Tinnitus severity was available in >99.7% of current tinnitus cases (N=26,201 and 22,247 in related and unrelated individuals respectively) and excluded those reporting “do not know” and “prefer not to answer”.

### Statistical analyses

- **Observational Associations**
Demographic characteristics were described for current tinnitus and controls using means and standard deviations for quantitative variables, and numbers and percentages for binary or categorical variables. Logistic regression models were utilised to investigate the association between current tinnitus status (binary outcome) and a) key demographic characteristics and b) the exposures listed in Table 1. Ordinal logistic regression was utilised to investigate the association between tinnitus severity and a) key demographic characteristics and b) the exposures listed in Table 1.

For all observational analyses, models were adjusted for age and sex and then additionally adjusted for Body Mass Index (BMI), material deprivation (measured as Townsend deprivation index) and smoking.

**Mendelian Randomisation (MR)**

We undertook 2-sample MR analyses to test the causal relationships between 23 exposure traits (Table 1) and current tinnitus and tinnitus severity as outcomes. The 2-sample MR analyses used summary level data from the BOLT-LMM Genome Wide Association Study (GWAS) of the current tinnitus and tinnitus severity (Loh et al., 2015). The known genome-wide significant SNPs for each exposure trait (Table 1) were extracted from the GWAS results to estimate the association of outcome and exposure-trait-SNP, whilst published coefficients from the primary GWAS were utilised for the association of exposure with exposure-trait-SNP (Beecham et al., 2013; Clarke et al., 2017; Consortium, 2010; Cornelis et al., 2015; Ehret et al., 2016; Epilepsies, 2018; Gormley et al., 2016; Hyde et al., 2016; Jones et al., 2019; Karlsson Linnér et al., 2019; Locke et al., 2015; Lu et al., 2016; Luciano et al., 2018; Mahajan et al., 2018; Malik et al., 2018; Okada et al., 2014; Okbay et al., 2016; Pardiñas et
To allow us to estimate the odds of current tinnitus per unit genetic change in the predictor we adjusted the betas and standard errors from the BOLT-LMM GWAS by the case control ratio of the current tinnitus measure.

Four 2-sample MR methods were performed using a custom pipeline: Inverse-variance weighting (IVW); MR-Egger; Weighted median (WM); Penalised weighted median (PWM). (Bowden et al., 2015; Bowden et al., 2016) Here, we present the IVW as our main analysis method. The MR-Egger, WM and PWM were used as sensitivity analyses to account for unidentified pleiotropy, which may bias our results. Horizontal pleiotropy occurs when the genetic variants related to the exposure of interest independently influence the outcome. IVW assumes there is either no horizontal pleiotropy under a fixed effects model or, if using a random effects model after detecting heterogeneity amongst the causal estimates, that the strength of the association between the genetic instruments and the exposure is not correlated with the magnitude of the pleiotropic effects (the InSIDE assumption) and that the pleiotropic effects have an average value of zero. MR-Egger estimates and adjusts for non-zero mean pleiotropy and therefore provides unbiased estimates if just the InSIDE assumption holds (Bowden et al., 2015).

In addition to the 2-sample MR, we also performed one-sample MR in the subset of unrelated individuals. One-sample methods were only used for a) confirming the IVW findings whilst fitting an appropriate model (e.g. logistic model for current tinnitus or an ordinal model for tinnitus severity) and b) testing
the role of smoking heaviness using the variant in CHRNA3-CHRN3 (rs1051730) in current tinnitus and tinnitus severity stratified by smoking status. All analyses were performed using Stata 16.1 software (College Station, US) or R version 3.5.0.

RESULTS

The demographics of the participants with tinnitus data within the UK Biobank are described in Table 2. The prevalence of current tinnitus within this cohort was 20% and severe tinnitus 3.8%. Current tinnitus was associated with older age, male gender, higher deprivation, higher adiposity (BMI, body fat percentage and waist hip ratio) and ever smoking status. There was a strong observational relationship between self-reported difficulty hearing and current tinnitus with hearing aid users having 4.09 higher odds of current tinnitus [95% Confidence Interval (CI) 3.81, 4.39]). Lower odds of current tinnitus were found in individuals with higher educational attainment, greater intelligence scores and higher caffeine and alcohol intake. Several diseases were associated with higher odds of current tinnitus, including major depression, migraine, rheumatoid arthritis, osteoarthritis, stroke and epilepsy (Table 2). Type 2 diabetes was associated with current tinnitus, but this was attenuated after adjustment for BMI. Personality traits were also associated with higher odds of reporting current tinnitus, including being an evening person, a risk taker or having a higher neuroticism score.

MR Provides Evidence That Several Factors Predict Current Tinnitus
Two-sample Mendelian randomisation demonstrated that 7 out of 23 factors predicted current tinnitus at $P<0.05$.

The strongest causal relationship was between self-reported difficulty hearing and current tinnitus, with a genetic liability for hearing difficulty associated with higher odds of current tinnitus (OR: 8.65 [95% CI: 6.12, 12.23], Figure 2a).

MR provided evidence that other factors cause current tinnitus (Figure 2b). These included personality and behavioural type traits. For example, a higher genetic liability for major depressive disorder was associated with higher odds of current tinnitus, with a doubling in the genetic liability of major depression associated with 1.26 [95%CI: 1.06, 1.50]. Similarly, higher neuroticism as determined by the Eysenck Personality Index also caused higher odds of current tinnitus (OR: 1.48 [95% CI: 1.28, 1.71]). Conversely, a morning chronotype was associated with lower odds of tinnitus (OR: 0.94 [95%CI: 0.90, 0.98]). Longer educational duration was associated with lower odds of current tinnitus. A one SD longer duration (~5 years) in education caused lower odds of current tinnitus (OR: 0.74 [95%CI: 0.63, 0.88]).

Higher blood pressure was associated with higher odds of current tinnitus, with a genetically predicted 1 mmHg higher diastolic blood pressure causing 1.01 higher odds [95% CI: 1.00, 1.02] of current tinnitus. Systolic blood pressure findings were directionally consistent, but the effect estimates crossed the null (OR: 1.007 [95%CI: 0.999, 1.014], $P=0.07$).
Two sample MR suggested that higher caffeine consumption was associated with lower odds of current tinnitus. This was further investigated within the one sample setting and findings were confirmed within caffeinated beverage drinkers, with a one SD (approx. 2 cups) higher genetically instrumented caffeine consumption associated with 0.63 lower odds [95% CI: 0.43, 0.92] of current tinnitus. No association was observed in individuals reporting no caffeinated beverage consumption.

One sample MR provided some tentative evidence for the role of increased smoking in predicting current tinnitus. In “ever” smokers the odds of current tinnitus were higher per genetically instrumented higher number of cigarettes per day (CPD) (OR: 1.94 [95%CI: 0.97, 3.90], \( P=0.063 \)). There was no evidence that the CPD Genetic Risk Score (GRS) was associated with current tinnitus in never smokers (OR: 1.00 [95%CI: 0.98, 1.01], \( P=0.60 \)).

Results were directionally consistent when using the different 2-sample MR methods that are more robust to pleiotropy, with no evidence of horizontal pleiotropy for those exposures associated with current tinnitus (Supplementary Table 1;Table 3).

**Associations Between Tinnitus Severity and Many Exposures**

The prevalence of moderate or severe tinnitus within this group was 23% and severe tinnitus only 3.8%. Several characteristics predict more severe tinnitus including older age, female gender, higher adiposity (BMI, body fat percentage and waist-hip ratio), deprivation, poorer hearing, lower educational attainment, former or current smoking, using a hearing aid and neuroticism. Several comorbidities were also predictive of tinnitus severity, including stroke, type 2 diabetes, bipolar affective disorder, major
depression, migraine, osteoarthritis, rheumatoid arthritis, schizophrenia and epilepsy (Table 4).

Association between Schizophrenia, Neuroticism and Tinnitus Severity

Two-sample Mendelian randomisation demonstrated that 2 out of 23 factors tested predicted tinnitus severity. Neuroticism as determined by Eysenck personality index and schizophrenia were predictive of higher tinnitus severity (Supplementary Table 1). A one standard deviation higher genetically predicted neuroticism score was associated with 1.15 (95%CI: 1.06, 1.26) higher odds of more severe tinnitus. When this was tested in the unrelated subset using one-sample approaches and an ordinal regression model, the odds of higher severity were 1.50 higher [95%CI: 1.21, 1.85] per SD higher genetically instrumented neuroticism score. Whilst for schizophrenia a one SD increase in the schizophrenia GRS in unrelated individuals was associated with higher odds of tinnitus severity (OR: 1.03 [95%CI: 1.01, 1.05], P=0.007). The association with schizophrenia remained when known cases of schizophrenia were excluded (OR: 1.03 [95%CI: 1.01, 1.05], P=0.008). Evidence for other predictors causing more severe tinnitus was limited (Supplementary Table 1). Results were directionally consistent when using the different 2-sample MR methods that are more robust to pleiotropy, with no evidence of horizontal pleiotropy for those exposures associated with tinnitus severity (Supplementary Table 1).

One sample MR provided tentative evidence that smoking heaviness causes higher odds of severe tinnitus in “ever” smokers (OR: 2.38 [95%CI: 0.91, 6.23], P=0.076). There was no evidence of an association between the CPD GRS and tinnitus severity in never smokers (OR: 1.00 [95%CI: 0.98, 1.02], P=0.89).


DISCUSSION

Statement Of Principal Findings

This study in 129,731 individuals in UK Biobank has investigated a range of factors including demographics, behavioural traits, education and comorbidities associated with tinnitus and its severity, confirming many previous observational findings and providing causal inference using the genetic approach of Mendelian randomisation. The use of MR is novel in the study of tinnitus and it expands our knowledge about which of the associated factors have a causal relationship with tinnitus. Here, we provide evidence that self-reported difficulty hearing, behavioural and psychiatric traits, blood pressure and education are involved in causing current tinnitus, whilst higher genetic liabilities for neuroticism and schizophrenia predict tinnitus severity.

Comparison with other studies

The observational findings reported in this study are consistent with the previous literature (Devinsky, 2004; Glicksman et al., 2014; Gudwani et al., 2017; Kim HJ, 2015; Lasisi et al., 2010; Mahboubi et al., 2013; Martinez et al., 2015; McCormack, Edmondson-Jones, Fortnum, et al., 2014; Mohamad et al., 2015; Negrila-Mezei et al., 2011; Nondahl et al., 2011; Nondahl et al., 2002; Ralli et al., 2018; Rodriguez-Caseroa et al., 2005; Shargorodsky et al., 2010; Sindhusake et al., 2003; Sindhusake et al., 2004; Stohler et al., 2019; Zacharia et al., 2014). Previous evidence for the association between gender and tinnitus is contradictory (Bhatt et al., 2017; Nondahl et al., 2011; Nondahl et al., 2002). Here, males had higher odds of reporting current tinnitus but reported lower severity. In this study, we used MR for the first time to identify predictors which may play a causal role in tinnitus development. Historically, hearing loss has
long been considered and acknowledged as a significant risk factor for tinnitus (Kim HJ, 2015; Nondahl et al., 2011; Shargorodsky et al., 2010; Sindhusake et al., 2003). Confirming the strong causative association evident with MR provides validity to the other associations observed. The MR method also provided evidence for neuroticism and major depression causing current tinnitus, with a higher genetic liability to neuroticism also associated with more severe tinnitus. Additionally, MR demonstrated that being a morning person (morning-chronotype), higher caffeine intake and longer time in education were protective factors for current tinnitus, confirming previous observational evidence (Glicksman et al., 2014; McCormack, Edmondson-Jones, Mellor, et al., 2014; Shargorodsky et al., 2010; Toplu et al., 2014; Zacharia et al., 2014). Higher blood pressure, which was a known risk factor from previous evidence (Figueiredo et al., 2015; Lasisi et al., 2010; Lin et al., 2016; Negrila-Mezei et al., 2011), was causally linked to current tinnitus, suggesting that lowering blood pressure in hypertensive individuals may help alleviate tinnitus. Similar, our study provided evidence that history of smoking was causal of higher tinnitus severity thus smoking cessation or reduction may help patients presenting with bothersome tinnitus.

For many comorbidities with robust observational associations, there was no evidence that they caused current tinnitus. This suggests that the observational associations are driven by either unmeasured or unaccounted for confounding factors or are a consequence of tinnitus and not causative of it. For example, comorbidities associated with tinnitus could be linked to a stronger underlying causative factor such as hearing loss or mental illness (Bhatt et al., 2017; Emamifar et al., 2016; Nondahl et al., 2011). The evidence for this is inconclusive at the present time but as further patterns of genetic association are identified it seems possible these comorbidities may not
present as independent causative risk factors. Furthermore, several predictors were
associated observationally with tinnitus severity but there was limited evidence that
they causally influenced tinnitus severity. The MR to identify factors which cause
alterations in tinnitus severity was limited by power, as this data was only available in
the 22,293 current tinnitus cases.

**Strengths And Weaknesses Of The Study**

Our study utilises the UK Biobank which is a large, population-base prospective study
that allows detailed analysis of genetic and non-genetic determinants for tinnitus and
its severity (Sudlow et al., 2015). The tinnitus data is only available in a subset of
individuals in the UK Biobank, which could introduce selection bias and influence our
observational and MR findings. However, these biases are likely to bias our results
towards the null hypothesis and therefore the true effect sizes may be larger than
reported (Tyrrell et al., 2020).

The perception of tinnitus is influenced by several factors such as psychological and
emotional interplay (McCormack, Edmondson-Jones, Fortnum, et al., 2014), and in
observational studies is difficult to determine to what extent associations are driven by
unmeasured psychological confounders. Utilising MR we are able to estimate effects
in the absence of these confounding factors, shedding light into causal risk factors for
tinnitus.

The UK Biobank had a low response rate (6%) to the baseline survey and therefore it
is not population representative, but it is considered that the risk factor associations
are still generalisable to the UK population (Batty et al., 2020). Moreover, the reliability
of the Biobank responses about tinnitus is not known and the data used for our analysis only represents a snapshot of the symptoms at initial assessment, and it does not capture in detail certain relevant characteristics such as pitch, duration, whether it is intermittent or permanent (Cederroth et al., 2019). Our analysis includes individuals with mild tinnitus, suggesting that some of the included participants may have experienced only intermittent tinnitus and/or would not or had not developed an intractable tinnitus.

Some of the variants utilised in MR (e.g. hearing difficulty) were discovered using UK Biobank, which has the potential to induce biases into the data, especially winner’s curse, which can lead to underestimation of the true causal effects (Burgess et al., 2016). Where possible, GWAS studies excluding the UK Biobank data were utilised (19 out of 23 predictors).

**Meaning Of The Study**

There was evidence that psychological factors (neuroticism) and psychiatric disorders (major depression) play a causal role in current tinnitus and a higher genetic liability to neuroticism was also indicated to cause more severe tinnitus. This suggests and supports the potential role of previously proposed treatment strategies such as counselling and Cognitive Behavioural Therapy (CBT) in the management of tinnitus (Martinez-Devesa et al., 2010).

The association between schizophrenia and tinnitus severity must be interpreted with caution as it is difficult to differentiate between tinnitus and auditory hallucinations commonly exhibited by schizophrenic patients (Dölberg et al., 2008). However, the
findings remain consistent when excluding known schizophrenic patients from the analyses suggesting that the relationship between schizophrenia and tinnitus severity is not solely due to presence of schizophrenia. It is possible that people with a higher genetic liability to schizophrenia without the condition experience more auditory hallucinations, although further work would be needed to test this.

Genetic evidence suggested several factors are causative for current tinnitus (e.g. smoking, high blood pressure), suggesting that clinicians could consider such risk factors when enquiring about the patient’s history. Identification of high-risk patients who are likely to require more intensive treatment for their tinnitus, can anticipate their need for a more comprehensive multi-disciplinary approach. These patients could benefit from the correction of modifiable risk factors such as high BMI, smoking and hypertension.

Unanswered Questions And Future Research

Our study demonstrates how MR can provide significant insight into the risk factors for tinnitus. As further GWAS become available in the literature, the existing predictors could be retested in higher-powered MR studies, and other predictors could be evaluated showing new causal pathways. Likewise, GWAS with audiometric assessment of hearing would be welcome to corroborate results of our analysis using hearing SNPs based on self-reported hearing difficulty.

Our study could be used to inform future research on therapeutic approaches to target the physical and psychological risk factors for tinnitus. Randomized Controlled Trials (RCTs) to test interventions would provide the best evidence, but their ethical
implications and feasibility could be challenging, for example when testing the role of mental health treatments in tinnitus.

Larger sample sizes with data on tinnitus severity would be required to infer causal risk factors for severe tinnitus using MR approaches.

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Transparency Statement: JT affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Data Sharing: Data from UK Biobank (https://www.ukbiobank.ac.uk/) is available to bona fide researchers on application. This research has been conducted using the UK Biobank Resource under Application number 19189. Results from UK Biobank are routinely disseminated to study participants via the study website.

List Of Abbreviations:
References

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**Figures**

**Figure 1: The Principles Of Mendelian Randomisation.**

The key assumptions are a) $Z$, the instrumental variable, should be robustly associated with the exposure $X$; b) $Z$ should not be associated with the U (confounders) of the $X$-$Y$ association; c) the only path from $Z$ to the outcome ($Y$) is through $X$. The dotted lines represent potential violations of assumptions (b) and (c).

**Figure 2: Dot Plot Representing The Odds Of Current Tinnitus In Observational And Genetic (MR) Analyses.**

Fig. 2. Dot plot representing the odds of current tinnitus in observational and genetic (MR) analyses.
<table>
<thead>
<tr>
<th>Exposure trait</th>
<th>Category</th>
<th>Evidence observationally associated with tinnitus</th>
<th>Number of SNPs utilised in 2-sample MR</th>
<th>Primary GWAS reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Anthropometric</td>
<td>Nondahl et al., 2011.</td>
<td>72</td>
<td>Locke et al., 2015</td>
</tr>
<tr>
<td>Body fat percentage</td>
<td>Anthropometric</td>
<td>Evidence of association between BMI and tinnitus</td>
<td>10</td>
<td>Lu et al., 2016</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>Anthropometric</td>
<td>Evidence of association between BMI and tinnitus</td>
<td>345</td>
<td>Puelit et al., 2018</td>
</tr>
<tr>
<td>(adjusted for BMI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Behavioural</td>
<td>Nondahl et al., 2011.</td>
<td>8</td>
<td>Clarke et al., 2017</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Behavioural</td>
<td>Glicksman et al., 2014, St Claire et al., 2010</td>
<td>6</td>
<td>Cornelis et al, 2015</td>
</tr>
<tr>
<td>Chronotype</td>
<td>Behavioural</td>
<td>Zacharia et al., 2014, Toplu et al., 2014</td>
<td>46</td>
<td>Jones et al., 2019</td>
</tr>
<tr>
<td>Risk taking</td>
<td>Behavioural</td>
<td>McCormack et al., 2014</td>
<td>13</td>
<td>Karlsson Linner et al., 2019</td>
</tr>
<tr>
<td>Smoking</td>
<td>Behavioural</td>
<td>Shargorodsky et al., 2010, Nondahl et al., 2011, Mahboubi et al., 2013, Kim et al., 2015</td>
<td>4</td>
<td>The Tobacco and Genetics Consortium, 2010</td>
</tr>
<tr>
<td>Stroke</td>
<td>Cardiovascular and metabolic markers</td>
<td>Huang et al., 2017</td>
<td>6</td>
<td>Malik et al., 2018</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Cardiovascular and metabolic markers</td>
<td>Negrila-Mezei et al., 2011</td>
<td>89</td>
<td>Mahajan et al., 2018</td>
</tr>
<tr>
<td>Educational attainment</td>
<td>Education and cognition</td>
<td>Shargorodsky et al., 2010, Kim et al., 2015</td>
<td>69</td>
<td>Okbay et al., 2016</td>
</tr>
<tr>
<td>Intelligence</td>
<td>Education and cognition</td>
<td>Mohamad et al., 2015, Gudwani et al., 2017</td>
<td>14</td>
<td>Sniekers et al., 2017</td>
</tr>
<tr>
<td>Depression</td>
<td>Psychological and neurological conditions</td>
<td>McKenna et al., 1991, Langenbach et al., 2005, Krog et al., 2010, Nondahl et al., 2011, Kim et al., 2015, Bhatt et al, 2017</td>
<td>17 and 38</td>
<td>Hyde et al., 2016 and Wray et al., 2018</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>Psychological and neurological conditions</td>
<td>McCormack et al., 2014, Langguth et al., 2007</td>
<td>116</td>
<td>Luciano et al., 2017</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Psychological and neurological conditions</td>
<td>Dölberg et al., 2008</td>
<td>137</td>
<td>Pardíñas et al., 2018</td>
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<tr>
<td>Migraine</td>
<td>Other diseases</td>
<td>Sindhusake et al., 2003, Sindhusake et al., 2004, Stohler et al., 2019</td>
<td>33</td>
<td>Gormley et al., 2016</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Other diseases</td>
<td>Kim et al., 2015</td>
<td>5</td>
<td>Zeggini et al, 2012</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Other diseases</td>
<td>Emamifar et al., 2016, Kim et al., 2015</td>
<td>69</td>
<td>Okada et al., 2014</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Other diseases</td>
<td>Devinsky et al., 2004</td>
<td>20</td>
<td>International League Against Epilepsy, 2018</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Other diseases</td>
<td>Ralli et al., 2018, Rodriguez-Caseroa et al., 2004</td>
<td>46</td>
<td>Beecham et al., 2013</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Hearing</td>
<td>Sindhusake et al., 2003, Shargorodsky et al., 2010, Nondahl et al., 2011, Kim et al., 2015</td>
<td>41</td>
<td>Wells et al., 2019</td>
</tr>
</tbody>
</table>

This table provides information on the previous published evidence for our predictors association with tinnitus and the details of the primary genome wide association study (GWAS) used for the genetic predictors in our study.

<table>
<thead>
<tr>
<th>Demographic/Exposure</th>
<th>Current tinnitus</th>
<th>No tinnitus reported</th>
<th>Odds of current tinnitus per unit change in demographic variable*</th>
<th>P-value</th>
<th>Odds of current tinnitus per unit change in demographic variable†</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22,293</td>
<td>88,474</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age at recruitment (SD)</td>
<td>59.4 (7.4)</td>
<td>57.3 (8.1)</td>
<td>1.04 (1.03, 1.04)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.04 (1.03, 1.04)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>12,084 (54.2)</td>
<td>39,042 (44.1)</td>
<td>1.47 (1.43, 1.52)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.45 (1.40, 1.49)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Mean Body Mass Index (BMI) (SD)</td>
<td>27.6 (4.8)</td>
<td>27.2 (4.7)</td>
<td>1.01 (1.01, 1.01)</td>
<td>3x10⁻¹³</td>
<td>1.01 (1.01, 1.01)</td>
<td>3x10⁻⁹</td>
</tr>
<tr>
<td>Mean Townsend deprivation index (SD)</td>
<td>-1.20 (2.9)</td>
<td>-1.41 (2.8)</td>
<td>1.03 (1.03, 1.04)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.03 (1.02, 1.04)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Has a degree, N (%)</td>
<td>9,778 (43.9)</td>
<td>44,589 (50.4)</td>
<td>0.80 (0.77, 0.82)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>0.82 (0.79, 0.84)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Mean fluid intelligence score (SD)</td>
<td>6.0 (2.1)</td>
<td>6.2 (2.1)</td>
<td>0.95 (0.94, 0.96)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>0.95 (0.94, 0.96)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (SD)</td>
<td>87 (14)</td>
<td>86 (13)</td>
<td>1.02 (1.01, 1.04)</td>
<td>4x10⁻⁶</td>
<td>0.99 (0.98, 1.01)</td>
<td>0.39</td>
</tr>
<tr>
<td>Mean systolic blood pressure (SD)</td>
<td>147 (24)</td>
<td>143 (24)</td>
<td>1.01 (1.00, 1.03)</td>
<td>0.049</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.19</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, N (%)</td>
<td>11,111 (49.8)</td>
<td>48,571 (54.9)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Former, N (%)</td>
<td>8,881 (39.8)</td>
<td>31,173 (35.2)</td>
<td>1.12 (1.09, 1.16)</td>
<td>2x10⁻¹²</td>
<td>1.10 (1.07, 1.14)</td>
<td>6x10⁻⁹</td>
</tr>
<tr>
<td>Current, N (%)</td>
<td>1,990 (8.9)</td>
<td>7,628 (8.6)</td>
<td>1.14 (1.08, 1.20)</td>
<td>3x10⁻⁴</td>
<td>1.08 (1.03, 1.15)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cigarettes per day (SD)</td>
<td>7.7 (11.7)</td>
<td>6.2 (10.3)</td>
<td>1.01 (1.01, 1.01)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.004 (1.001, 1.007)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean alcohol units per day</td>
<td>0.27 (1.26)</td>
<td>0.28 (1.23)</td>
<td>0.93 (0.92, 0.94)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>0.93 (0.91, 0.94)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Risk taker, N (%)</td>
<td>5,917 (26.5)</td>
<td>21,862 (24.7)</td>
<td>1.08 (1.04, 1.11)</td>
<td>4x10⁻⁵</td>
<td>1.06 (1.02, 1.09)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean body fat percentage (SD)</td>
<td>31.0 (8.6)</td>
<td>31.5 (8.5)</td>
<td>1.01 (1.01, 1.01)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.01 (1.00, 1.01)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Mean waist hip ratio (SD)</td>
<td>0.89 (0.09)</td>
<td>0.87 (0.09)</td>
<td>2.15 (1.72, 2.68)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.32 (1.01, 1.71)</td>
<td>0.040</td>
</tr>
<tr>
<td>Cups of caffeinated coffee per day (SD)</td>
<td>1.94 (2.09)</td>
<td>1.99 (2.06)</td>
<td>0.98 (0.97, 0.99)</td>
<td>6x10⁻⁴</td>
<td>0.98 (0.97, 0.99)</td>
<td>3x10⁻⁷</td>
</tr>
<tr>
<td>Morning person chronotype, N (%)</td>
<td>12,227 (54.9)</td>
<td>50,474 (57.1)</td>
<td>0.88 (0.85, 0.91)</td>
<td>2x10⁻¹⁵</td>
<td>0.89 (0.86, 0.92)</td>
<td>8x10⁻¹³</td>
</tr>
<tr>
<td>Stroke, N (%)</td>
<td>686 (3.1)</td>
<td>1,959 (2.2)</td>
<td>1.18 (1.08, 1.29)</td>
<td>0.0003</td>
<td>1.13 (1.03, 1.24)</td>
<td>0.008</td>
</tr>
<tr>
<td>Type 2 diabetes, N (%)</td>
<td>907 (4.1)</td>
<td>2,633 (3.0)</td>
<td>1.11 (1.03, 1.20)</td>
<td>0.007</td>
<td>1.04 (0.96, 1.13)</td>
<td>0.36</td>
</tr>
<tr>
<td>Bipolar, N (%)</td>
<td>252 (1.1)</td>
<td>660 (0.8)</td>
<td>1.80 (1.55, 2.09)</td>
<td>9x10⁻¹⁵</td>
<td>1.72 (1.48, 2.00)</td>
<td>2x10⁻¹²</td>
</tr>
<tr>
<td>Major depression, N (%)</td>
<td>6,023 (27.0)</td>
<td>20,022 (22.6)</td>
<td>1.50 (1.44, 1.55)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.45 (1.40, 1.51)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Mean Neuroticism score (SD)</td>
<td>4.9 (3.4)</td>
<td>4.1 (3.2)</td>
<td>1.09 (1.09, 1.10)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.09 (1.08, 1.10)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Schizophrenia, N (%)</td>
<td>49 (0.2)</td>
<td>150 (0.2)</td>
<td>1.25 (0.90, 1.73)</td>
<td>0.18</td>
<td>1.11 (0.79, 1.55)</td>
<td>0.55</td>
</tr>
<tr>
<td>Migraine, N (%)</td>
<td>840 (3.8)</td>
<td>2,669 (3.0)</td>
<td>1.46 (1.35, 1.59)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.47 (1.36, 1.60)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
</tbody>
</table>
P > 0.05 it indicates no evidence of horizontal pleiotropy.

The MR Egger method accounts for pleiotropy (were the genetic variant may not be solely associated with the exposure) and here we report the intercept p-value from these analyses, if P > 0.05 it indicates no evidence of horizontal pleiotropy.

Table 3: Summary of the 2-sample Inverse Variance Weighted Results from Mendelian Randomisation (MR) analyses for exposures at P < 0.05

<table>
<thead>
<tr>
<th>Exposure in MR Analyses</th>
<th>Tinnitus outcome</th>
<th>Odds Ratio (95% Confidence Intervals) [OR (95%CI)]</th>
<th>P-Value</th>
<th>Evidence of pleiotropy?**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported hearing difficulty</td>
<td>Current tinnitus</td>
<td>6.85 (6.12, 12.23)</td>
<td>4x10^-16</td>
<td>No: Egger intercept p = 0.84</td>
</tr>
<tr>
<td>Major depression</td>
<td>Current tinnitus</td>
<td>1.26 (1.06, 1.50)</td>
<td>0.013</td>
<td>No: Egger intercept p = 0.96</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>Current tinnitus</td>
<td>1.48 (1.28, 1.71)</td>
<td>6x10^-7</td>
<td>No: Egger intercept p = 0.82</td>
</tr>
<tr>
<td>Years in education</td>
<td>Current tinnitus</td>
<td>0.74 (0.63, 0.88)</td>
<td>0.0009</td>
<td>No: Egger intercept p = 0.35</td>
</tr>
<tr>
<td>Cups of caffeinated coffee per day*</td>
<td>Current tinnitus</td>
<td>0.89 (0.83, 0.95)</td>
<td>0.022</td>
<td>No: Egger intercept p = 0.15</td>
</tr>
<tr>
<td>Morning person chronotype</td>
<td>Current tinnitus</td>
<td>0.94 (0.90, 0.98)</td>
<td>0.007</td>
<td>No: Egger intercept p = 0.10</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>Current tinnitus</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.032</td>
<td>No: Egger intercept p = 0.48</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>Tinnitus severity†</td>
<td>1.15 (1.06, 1.26)</td>
<td>0.002</td>
<td>No: Egger intercept p = 0.55</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Tinnitus severity†</td>
<td>1.02 (1.00, 1.04)</td>
<td>0.023</td>
<td>No: Egger intercept p = 0.51</td>
</tr>
</tbody>
</table>

*Note this is per one unit higher variable for continuous variables and for cases versus controls for binary predictors adjusted for age and sex, with the exception of blood pressure, where we provide a per standard deviation (SD) change (13 mmHg for diastolic and 24 for systolic).

† As above with additional adjustment for body mass index, socioeconomic position (SEP) and smoking status.

** The MR Egger method accounts for pleiotropy (were the genetic variant may not be solely associated with the exposure) and here we report the intercept p-value from these analyses, if P > 0.05 it indicates no evidence of horizontal pleiotropy.
Table 4: Observational Associations of the Key Demographics and Exposures with Tinnitus Severity

<table>
<thead>
<tr>
<th>Demographic/Exposure</th>
<th>Odds of higher tinnitus severity per unit change in demographic variable*</th>
<th>P-value</th>
<th>Odds of higher tinnitus severity per unit change in demographic variable†</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at recruitment</td>
<td>1.01 (1.00, 1.01)</td>
<td>7x10⁻⁵</td>
<td>1.01 (1.00, 1.01)</td>
<td>6x10⁻⁵</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.78 (0.74, 0.82)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>0.75 (0.71, 0.79)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td><strong>Body Mass Index (BMI)</strong></td>
<td>1.02 (1.01, 1.03)</td>
<td>2x10⁻¹³</td>
<td>1.02 (1.01, 1.02)</td>
<td>8x10⁻¹¹</td>
</tr>
<tr>
<td>Townsend deprivation index</td>
<td>1.03 (1.02, 1.04)</td>
<td>1x10⁻¹²</td>
<td>1.02 (1.01, 1.03)</td>
<td>3x10⁻⁷</td>
</tr>
<tr>
<td>Has a degree</td>
<td>0.82 (0.78, 0.86)</td>
<td>1x10⁻¹⁵</td>
<td>0.86 (0.82, 0.90)</td>
<td>6x10⁻⁹</td>
</tr>
<tr>
<td>Fluid intelligence score</td>
<td>0.95 (0.94, 0.06)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>0.96 (0.95, 0.97)</td>
<td>3x10⁻¹¹</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.999 (0.998, 1.002)</td>
<td>0.99</td>
<td>0.997 (0.995, 0.999)</td>
<td>0.009</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.999 (0.997, 0.999)</td>
<td>0.011</td>
<td>0.997 (0.996, 0.998)</td>
<td>3x10⁻⁶</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>1.19 (1.12, 1.25)</td>
<td>3x10⁻¹⁰</td>
<td>1.15 (1.09, 1.22)</td>
<td>2x10⁻⁷</td>
</tr>
<tr>
<td>Current</td>
<td>1.35 (1.23, 1.48)</td>
<td>1x10⁻¹⁰</td>
<td>1.29 (1.17, 1.41)</td>
<td>9x10⁻⁸</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>1.01 (1.01, 1.01)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.01 (1.00, 1.01)</td>
<td>0.002</td>
</tr>
<tr>
<td>Alcohol units per day</td>
<td>1.01 (0.98, 1.03)</td>
<td>0.56</td>
<td>1.00 (0.98, 1.02)</td>
<td>0.99</td>
</tr>
<tr>
<td>Risk taker</td>
<td>1.10 (1.04, 1.16)</td>
<td>0.001</td>
<td>1.08 (1.01, 1.13)</td>
<td>0.028</td>
</tr>
<tr>
<td>Body fat percentage</td>
<td>1.02 (1.01, 1.02)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.02 (1.01, 1.02)</td>
<td>1x10⁻⁵</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>5.59 (3.87, 8.06)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>3.08 (1.99, 4.76)</td>
<td>4x10⁻⁷</td>
</tr>
<tr>
<td>Cups of caffeinated coffee per day</td>
<td>0.99 (0.98, 1.01)</td>
<td>0.40</td>
<td>0.99 (0.97, 1.00)</td>
<td>0.08</td>
</tr>
<tr>
<td>Morning person chronotype</td>
<td>0.94 (0.89, 0.99)</td>
<td>0.021</td>
<td>0.95 (0.90, 1.01)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.29 (1.12, 1.49)</td>
<td>0.0006</td>
<td>1.20 (1.04, 1.40)</td>
<td>0.014</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1.33 (1.18, 1.51)</td>
<td>8x10⁻⁶</td>
<td>1.20 (1.05, 1.36)</td>
<td>0.007</td>
</tr>
<tr>
<td>Bipolar</td>
<td>2.44 (1.92, 3.09)</td>
<td>2x10⁻¹³</td>
<td>2.30 (1.80, 2.93)</td>
<td>2x10⁻¹³</td>
</tr>
<tr>
<td>Major depression</td>
<td>1.65 (1.55, 1.75)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.59 (1.50, 1.69)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Mean Neuroticism score (SD)</td>
<td>1.12 (1.11, 1.13)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.12 (1.11, 1.13)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2.11 (1.23, 3.61)</td>
<td>0.007</td>
<td>1.85 (1.06, 3.22)</td>
<td>0.03</td>
</tr>
<tr>
<td>Migraine</td>
<td>1.26 (1.10, 1.43)</td>
<td>0.0006</td>
<td>1.25 (1.10, 1.43)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.36 (1.15, 1.62)</td>
<td>0.0004</td>
<td>1.29 (1.08, 1.53)</td>
<td>0.005</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.32 (1.24, 1.40)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.26 (1.18, 1.34)</td>
<td>1x10⁻¹²</td>
</tr>
<tr>
<td>Temporomandibular joint disorders</td>
<td>0.39 (0.14, 1.07)</td>
<td>0.068</td>
<td>0.35 (0.13, 0.98)</td>
<td>0.045</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1.60 (1.31, 1.96)</td>
<td>4x10⁻⁶</td>
<td>1.53 (1.25, 1.88)</td>
<td>4x10⁻⁵</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1.03 (0.68, 1.56)</td>
<td>0.88</td>
<td>0.94 (0.61, 1.43)</td>
<td>0.77</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1.72 (1.35, 2.19)</td>
<td>1x10⁻⁵</td>
<td>1.60 (1.25, 2.04)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>1.46 (1.09, 1.96)</td>
<td>0.01</td>
<td>1.43 (1.06, 1.92)</td>
<td>0.019</td>
</tr>
<tr>
<td>Mean hearing left ear</td>
<td>1.07 (1.06, 1.08)</td>
<td>&lt;1x10⁻¹⁵</td>
<td>1.06 (1.05, 1.07)</td>
<td>&lt;1x10⁻¹⁵</td>
</tr>
<tr>
<td></td>
<td>Mean hearing right ear</td>
<td>Hearing aid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.07 (1.06, 1.08)</td>
<td>1.88 (1.71, 2.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1x10^{-15}</td>
<td>&lt;1x10^{-15}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.06 (1.05, 1.07)</td>
<td>1.83 (1.66, 2.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1x10^{-15}</td>
<td>&lt;1x10^{-15}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note this is the odds ratio from an ordinal logistic regression model and is per one unit higher variable for continuous variables and for cases versus controls for binary predictors adjusted for age and sex.

† As above with additional adjustment for body mass index, socioeconomic position (SEP) and smoking status.