Insights into the aetiology of snoring from observational and genetic investigations in the UK Biobank

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Although snoring is common in the general population, its aetiology has been largely understudied. Here we report a genetic study on snoring (n ~ 408,000; snorers ~ 152,000) using data from the UK Biobank. We identify 42 genome-wide significant loci, with an SNP-based heritability estimate of ~10% on the liability scale. Genetic correlations with body mass index, alcohol intake, smoking, schizophrenia, anorexia nervosa and neuroticism are observed. Gene-based associations identify 173 genes, including DLEU7, MSRB3 and POC5, highlighting genes expressed in the brain, cerebellum, lungs, blood and oesophagus. We use polygenic scores (PGS) to predict recent snoring and probable obstructive sleep apnoea (OSA) in an independent Australian sample (n ~ 8000). Mendelian randomization analyses suggest a potential causal relationship between high BMI and snoring. Altogether, our results uncover insights into the aetiology of snoring as a complex sleep-related trait and its role in health and disease beyond it being a cardinal symptom of OSA.

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Snoring is the vibration of the upper airway structures that occurs during sleep and creates noise as the air passes in and out while breathing. Habitual snoring is common in the population, its overall prevalence increases with age and is higher in males (35–45%) than females (15–28%)\(^1\). Importantly, snoring is a hallmark of obstructive sleep apnoea (OSA), a sleep-related breathing disorder characterized by repeated episodes of complete or partial obstructions of the upper airway during sleep, despite the effort to breathe\(^1\). OSA is usually associated with a reduction in blood oxygen saturation and is often accompanied by associated daytime symptoms, such as excessive daytime sleepiness, fatigue and decreased cognitive function. Although the vast majority of patients with OSA exhibit snoring, a minority (20–25%) of patients with central sleep apnoea do not snore\(^2\) and it is estimated that sleep apnoea may occur in as many as 20–40% of the adult population that are snorers, leaving the remaining 60–80% of snorers in the category of habitual non-apnoeic benign snorers. Snoring has previously been associated with body mass index (BMI)\(^3,4\) as well as with the risk of cardiovascular disease\(^5\) and obesity\(^6\). Snoring has previously been associated with body mass index (BMI)\(^3,4\) as well as with the risk of cardiovascular disease\(^5\) and obesity\(^6\). Snorers. Snoring has previously been associated with body mass index (BMI)\(^3,4\) as well as with the risk of cardiovascular disease\(^5\) and obesity\(^6\). Snoring has previously been associated with body mass index (BMI)\(^3,4\) as well as with the risk of cardiovascular disease\(^5\) and obesity\(^6\). Snoring has previously been associated with body mass index (BMI)\(^3,4\) as well as with the risk of cardiovascular disease\(^5\) and obesity\(^6\).

**Results**

Snoring prevalence and risk factors. Our population-based discovery sample consisted of 408,317 individuals of white British ancestry from the UK Biobank. Participants in the sample were deemed as snoring ‘cases’ (37%) based on their report that a partner or housemate had complained to the participant about their snoring (see Methods and Table 1). Snoring was significantly associated with age (odds ratio (OR) = 1.011 [per year, 95% confidence interval (CI) 1.009–1.012]) and, to a greater extent, with sex (ORmales = 2.264 [2.212–2.316]). The prevalence of sleep apnoea was higher within the snorer group (Table 1). Furthermore, BMI, SES, smoking frequency and alcohol consumption frequency were also associated with snoring (Fig. 1a). Although snoring prevalence was higher in males, BMI was positively correlated with snoring prevalence in both males and females (Fig. 1b). A lower SES, as determined by both Townsend deprivation index and average household income, was associated with increased snoring in males only. Smoking frequency was positively correlated with snoring prevalence in females and, to a lesser extent, in males (Fig. 1a–c). In contrast, alcohol consumption frequency was correlated with snoring in males and, to a lesser extent, in females (Fig. 1a–d). We further identified other factors such as whole-body fat mass and sleep duration that are correlated with snoring (Supplementary Table 1).

**Discovery GWAS and SNP heritability.** We performed a GWAS study of snoring, taken as a dichotomous variable \((n = 408,317;\) cases \(\sim 152,000;\) controls \(\sim 256,000\)). After quality control (QC; see Methods), 11,010,159 genetic variants remained in the analysis. This uncovered 127 independent genome-wide significant associations across 41 genomic risk loci (Fig. 2a and Supplementary Fig. 1)\(^1\). Annotation for the top 15 risk loci is shown in Table 2 and a list of all genomic risk loci is given in Supplementary Data 1. The overall SNP heritability on the liability scale \((h^2_{SNP})\) was 9.9% \((SE = 0.39\%\).

**Genetic correlations.** The trait that showed the highest genetic correlation with habitual snoring was self-reported sleep apnoea \((r_G = 0.78, SE = 0.17, p\text{-value} = 3 \times 10^{-05}; ldsc \chi^2\text{-test};\) Supplementary Data 2). We also analysed the genetic correlation between snoring and three measures of overnight oxyhemoglobin saturation: average SpO\(_2\), minimum SpO\(_2\) saturation and percent of sleep with oxyhemoglobin saturation under 90% \((\text{Oxyc}90)\)\(^14\). Minimum SpO\(_2\) and Perc90, which are known proxies for sleep-disordered breathing, but not average SpO\(_2\) (which reflects changes in ventilation not necessarily related to sleep apnoea), showed moderate significant genetic correlations with snoring (Fig. 3). Other traits genetically correlated to snoring included BMI, whole-body fat mass, sodium in urine, mood swings, coronary artery disease, alcohol intake frequency, pulse rate, current tobacco smoking, heart disease, lung cancer, the ratio between forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC), neuroticism, subjective wellbeing and heart rate, among others. Traits showing a negative genetic correlation with snoring included schizophrenia, FVC, FEV1, fluid intelligence score, educational attainment, age at menarche, mean accumbens volume and anorexia nervosa. Overall, traits related to BMI, risk for psychiatric disease, lung function and heart disease were among those with the strongest evidence of association (Fig. 3 and Supplementary Data 2). Notably, pulse rate, whole-body fat mass and BMI were also phenotypically associated with snoring in this sample (see above and Supplementary Table 1).

**Sensitivity analysis.** We performed two follow-up sensitivity GWAS to explore the effects of BMI, adiposity and nonlinear effects on associated variants. The first sensitivity GWAS included BMI as a covariate, whereas the second included BMI, BMI\(^2\), age \(\times\) sex, age\(^2\) and whole-body fat mass. Both sensitivity analyses showed very similar results, with a genetic correlation of 0.9998 \((SE = 0.0002\)). We therefore focus below on the simple model adjusting only for BMI and basic covariates (see Methods). The results revealed 97 genome-wide significant SNPs across 34 genomic risk loci (Fig. 2a) with overall SNP heritability on the
for BMI (Fig. 3 and Supplementary Data 3). The genetic correlation between both the adjusted and unadjusted GWAS was high ($r_G = 0.923$, SE = 0.003, $p$-value = $1 \times 10^{-300}$), suggesting that a considerable amount of snoring predisposition is not fully explained by BMI.

### Table 1 Sample composition and descriptive statistics of UK Biobank discovery sample.

|                       | Female N (%) | Apnoea N (%) | Age mean (SD) | BMI mean (SD) |
|-----------------------|--------------|--------------|---------------|---------------|
| Cases (snorers)       | 63833 (40.74%) | 4510 (2.88%) | 57.01 (7.70)  | 28.67 (4.85)  |
| Controls              | 161775 (61.44%) | 1663 (0.63%) | 56.60 (8.21)  | 26.64 (4.52)  |
| Total                 | 225608 (53.72%) | 6173 (1.47%) | 56.75 (8.03)  | 27.39 (4.75)  |

$N$ — Sample sizes. Descriptive statistics were calculated only for the subset of the data with European or British ancestry.

### Positional, eQTL and gene-based test prioritization.

To gain insights into the functional consequences of individual genome-wide significant variants, we used positional and expression quantitative trait loci (eQTL) mapping, as well as genome-wide gene-based association analyses. From positional and eQTL mapping, we identified 149 protein-coding genes mapping to a genome-wide significant SNP. The nearest genes to the top signals included DLEU7 on chromosome 13 and MSRB3 on chromosome 12. In addition to DLEU7 and MSRB3, other compelling genes (prioritized by positional or eQTL mapping) for snoring included BCL11B, FTO, SMG6, ROBO2, NSUN3, SNAP91 and BCL2, which have previously been associated with smoking15,16; BLC11B, FTO17, RNA55P47117,18 and SN1D and NSUN3, previously associated with alcohol consumption15,17–19; FTO and SN1D, associated with coffee consumption20; LMO4 associated with insomnia21; and RNA55P471 with narcolepsy21,22. In addition, ROBO2 was previously associated with chronotype23,24 and multiple genes (DLEU7, MSRB3, FTO, ANAPC4, SMG6, SN1D, SIM1, KCNQ5, CEP120, MACF1, SNAP91 and BCL2) previously associated with musculoskeletal traits such as height and heel bone mineral density (Supplementary Data 1 and 2)25–28. Genome-wide gene-based association analysis identified 179 genes associated with snoring beyond genome-wide significance.
enrichment analyses of tissue expression data (Supplementary functional gene sets and pathways, we conducted gene-set mapped with Functional Mapping and Annotation of Genome- and psychiatric (Fig. 4 and Supplementary Data 1).

In summary, many of the mapped genes for snoring have been grouped into cardiometabolic, cognitive/neurological, respiratory including the lungs, blood, oesophagus, breast mammary, tibial nerve, and several areas of the brain, such as the cerebellum and hippocampus (Supplementary Fig. 3 and Supplementary Data 2).

Table 2 Top 15 genomic risk loci for snoring showing the top SNP for each locus.

| SNP      | Chr | Position | NEA | EA | MAF     | Nearest gene | gwasP     | β     | SE     |
|----------|-----|----------|-----|----|---------|--------------|-----------|-------|--------|
| rs592333 | 13  | 51,340,315 | G   | A  | 0.4423  | DLEU7        | 1.00E – 17 | –0.00906 | 0.001051 |
| rs10878269| 12  | 65,791,463 | T   | C  | 0.3499  | MSRB3        | 2.30E – 16 | –0.00886 | 0.001086 |
| rs16597598| 2   | 156,996,626 | A   | G  | 0.1163  | ACO73SS1.1   | 5.10E – 15 | –0.01189 | 0.001529 |
| rs230711 | 5   | 75,003,678  | C   | T  | 0.3956  | POC5         | 4.80E – 13 | 0.007667 | 0.00107 |
| rs2664299| 14  | 99,742,187  | C   | T  | 0.4145  | BCL11B       | 1.10E – 12 | 0.007503 | 0.001061 |
| rs13251292| 8   | 71,474,355  | G   | A  | 0.4145  | TRAMI        | 4.30E – 12 | –0.00737 | 0.001067 |
| rs57722984| 17  | 43,758,898  | G   | A  | 0.2654  | CHRNA5:RP11-105N13.4 (ncRNA) | 5.40E – 12 | –0.00843 | 0.00122 |
| rs725861 | 10  | 9,063,776   | G   | A  | 0.1938  | RPIP1-421.9.2 | 1.00E – 11 | –0.00908 | 0.001338 |
| rs1219849| 11  | 96,878,072  | A   | G  | 0.0825  | UBE2W1 (pseudogene) | 4.10E – 11 | –0.01226 | 0.00186 |
| rs796856741| 16  | 53,799,278  | GT  | G  | 0.4433  | FTO          | 4.70E – 11 | –0.00696 | 0.001059 |
| rs12429765| 13  | 40,745,860  | G   | A  | 0.493   | LINCO0332    | 6.20E – 11 | 0.0068 | 0.001051 |
| rs34811474| 4   | 25,408,838  | A   | G  | 0.2167  | ANAPC4       | 1.30E – 10 | 0.007996 | 0.001237 |
| rs7829639| 8   | 78,215,352  | G   | A  | 0.2972  | AC010524.2 (mRNA) | 1.40E – 10 | –0.00741 | 0.001155 |
| rs180107 | 17  | 67,930,772  | T   | A  | 0.3698  | AC002539.2 (mRNA) | 2.10E – 10 | –0.0068 | 0.00106 |
| rs11409890| 17  | 46,269,542  | TA  | T  | 0.4821  | SKAP1:RP11-456D7 | 2.20E – 10 | 0.006664 | 0.001061 |

(\(p < 2.636e – 6\); Bonferroni-corrected threshold for 18,971 tested genes) several of which were consistent with the mapped genes. After adjusting for BMI, 104 protein-coding genes were identified mapping to a genome-wide significant SNP from the positional and eQTL mapping, whereas 120 genes remained significantly associated with snoring, including both MSRB3 and DLEU7 (see Supplementary Fig. 2 and Supplementary Data 2 and 3). eQTL data obtained from Genotype-Tissue Expression (GTEx) highlighted significant SNPs that were associated with the expression of genes in several tissues including the lungs, blood, oesophagus, breast mammary, tibial nerve, and several areas of the brain, such as the cerebellum and hippocampus (Supplementary Fig. 3 and Supplementary Data 2).

In summary, many of the mapped genes for snoring have been previously associated with other traits and diseases, primarily grouped into cardiometabolic, cognitive/neurological, respiratory and psychiatric (Fig. 4 and Supplementary Data 1).

To further assess whether significant genes converged in functional gene sets and pathways, we conducted gene-set enrichment analyses of tissue expression data (Supplementary Fig. 3a). Genes expressed in blood vessel and tibial artery tissue were associated with snoring, even after adjusting for BMI (Supplementary Fig. 3b). Given these associations, and an observed genetic correlation between snoring and pulse rate (Supplementary Fig. 3b), we conducted a two-sample generalized summary-data-based MR (GSMR)\(^29\) to test for a possible causal relationship. The analysis suggested a one-way causal relationship in which snoring increased pulse rate (Supplementary Fig. 4). Further, we found the association between snoring and BMI, whole-body fat mass, blood pressure, major coronary heart disease and heart attack. GSMR results suggested a bidirectional causal relationship, with snoring exerting a causal effect on BMI, but also BMI exerting a causal effect on snoring, and a similar pattern was observed for heart attack. In addition, one-way causal relationships were seen for whole-body fat mass causing snoring and for snoring causing an increase in blood pressure (Supplementary Fig. 4). To control for possible confounding due to sample overlap, we conducted GSMR analyses using sex-stratified GWAS results (see Methods). The results supported causal relationships between BMI (and whole-body fat mass) causing snoring, whereas all
other associations did not reach statistical significance after controlling for multiple testing (Supplementary Table 2). We performed further sensitivity analyses using five different MR methods that test different assumptions (Fig. 5). The results of GSMR, inverse variance weighted (IVW-MR) and weighted median analyses supported a causal effect of BMI (and whole-body fat mass) on snoring. Notably, although the MR-Egger estimates did not reach statistical significance, the Egger intercept was not significantly different from zero.

Sex-stratified GWAS. Given the higher prevalence of snoring in males, we conducted GWAS analyses stratified by sex. These analyses identified 4 and 25 genome-wide significant SNPs for snoring in males and females, respectively. SNP heritability on the liability scale ($h^2_{SNP}$) was 8.77% (SE = 0.54%) and 12.42% (SE = 0.57%), respectively, for males and females (Table 3). In the sensitivity analyses, SNP heritability ($h^2_{SNP}$) was slightly lower after adjusting for BMI in both males 7.72% (SE = 0.56%) and females 10.85% (SE = 0.54%) (Table 3). We identified two loci (lead SNPs rs199797821 and rs200391180) with a significantly different effect size between sexes, although in the same direction. The cross-sex genetic correlation was high ($r_G = 0.914$, SE = 0.033, p-value = $1.91 \times 10^{-160}$), and effect sizes and directions for top hits were highly consistent in both the male and female samples (Supplementary Data 1 and Supplementary Fig. 5).

**Table 3 SNP-based heritability of snoring on the liability scale.**

| Trait                        | $h^2_{SNP}$ | SE    | $\lambda_{GC}$ | Intercept |
|------------------------------|-------------|-------|-----------------|-----------|
| Snoring                      | 9.9%        | 0.39% | 1.428           | 1.04 (0.01) |
| Snoring adj. for BMI         | 8.67%       | 0.39% | 1.368           | 1.03 (0.009) |
| Snoring males                | 8.77%       | 0.54% | 1.200           | 1.01 (0.007) |
| Snoring females              | 12.42%      | 0.57% | 1.254           | 1.02 (0.007) |
| Snoring adj. for BMI males   | 7.72%       | 0.56% | 1.200           | 1.01 (0.008) |
| Snoring adj. for BMI females | 10.85%      | 0.54% | 1.253           | 1.02 (0.007) |

LD score regression derived SNP-based heritability results. Estimates were transformed to the liability scale, assuming equal population and sample prevalence. $\lambda_{GC}$ is the genomic inflation factor and intercept is the LD score regression intercept.
Fig. 4 Snoring genes associated with other traits or diseases. a Venn diagram showing the nearest genes to the lead significant SNP per genomic risk loci identified for snoring, categorized according to previously reported association with other traits or diseases in the GWAS catalogue. b Significant gene-set enrichment analysis (hypergeometric test) based on all prioritized genes against gene sets defined by traits in the GWAS catalogue.
study that failed to identify an association between alcohol consumption and snoring in females compared with that in females. This is consistent with a previous study, tobacco smoking displayed a stronger association with snoring in females compared with males, a result consistent with our study, tobacco smoking displayed a stronger association with snoring in females compared with males. In both sexes, the effects of BMI, smoking and alcohol consumption have been previously reported in other studies. In males only. Considering that the analysis simultaneously accounted for the effects of BMI, tobacco smoking and alcohol consumption frequency, we speculate that the snoring-SES association might be mediated through factors that are associated with a lower SES and differ between males and females (e.g., work-related exposures). Nonetheless, whether SES is causally associated with snoring in males remains to be assessed. This would require well-powered genetic correlates of SES on independent samples. The differences in risk factor effect sizes between males and females might contribute to the overall observed sex difference in snoring prevalence. Future studies should leverage statistical genetics methods such as polygenic scoring or MR to further characterize the role of SES, smoking and alcohol-related phenotypes in snoring and OSA.

The sex differences described above motivated us to perform sex-stratified GWAS. The larger sample size of the female subgroup conferred more power to detect genetic associations in our analyses. Notably, we identified a higher snoring SNP-based heritability in females than in males and two loci that displayed statistically significant different effect sizes between sexes. Nonetheless, the observed high cross-sex genetic correlation and a high concordance in effect size and direction among top hits suggest that differences in sex-stratified GWAS might be due to power differences between the male and female subsamples rather than the existence of large-scale sex-specific genetic effects. Future studies should assess whether the loci with evidence of sex-specific effects are mediating the differential effects of SES, alcohol or tobacco consumption frequency between sexes.

Top genes identified from gene-based test analysis for snoring included DLEU7 and MSRB3. Previous reports have associated DLEU7 with heel bone mineral density, BMI, height, cardiovascular diseases, systolic blood pressure and pulmonary function decline (FEV). The association between snoring and sleep apnoea, potentially through a weakening (relaxation) effect in the jaw and pharyngeal muscles. Our study revealed that lower SES was associated with higher snoring prevalence in males only. Considering that the analysis simultaneously accounted for the effects of BMI, alcohol and tobacco consumption frequency, we speculate that the snoring-SES association might be mediated through factors that are associated with a lower SES and differ between males and females (e.g., work-related exposures). Nonetheless, whether SES is causally associated with snoring in males remains to be assessed. This would require well-powered genetic correlates of SES on independent samples. The differences in risk factor effect sizes between males and females might contribute to the overall observed sex difference in snoring prevalence. Future studies should leverage statistical genetics methods such as polygenic scoring or MR to further characterize the role of SES, smoking and alcohol-related phenotypes in snoring and OSA.

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genes and heel bone mineral density could be mediated by BMI due to the association between BMI and bone density documented previously. MSRB3 plays a relevant role in protein and lipid metabolism pathways, and has been associated with hip-height estimates, but also introduce collider bias. We have therefore reduced power for estimating genetic correlations or causality. We also observed moderate correlations with BMI, obesity and whole-body fat mass. Other relevant correlations included lung function, neurological, cardiovascular and psychiatric diseases, and traits such as alcohol consumption frequency and smoking. This is consistent with the observed phenotypic associations on the first part of this study. The high genetic correlation between snoring and smoking (rG = 0.923, SE = 0.003, p-value = 1 × 10−300) supports the idea that the genetic architecture of snoring cannot be explained simply by BMI. Notably, the genetic correlations between snoring and diseases such as asthma and allergic rhinitis, which are considered risk factors for sleep-disordered breathing, do not reach statistical significance. This could imply that the association of atopic diseases and sleep-disordered breathing is not mediated through genetics, but future genome-wide hits) that the GWAS for self-reported sleep apnoea has in the UK Biobank. Our analyses suggest that a GWAS for snoring captures a substantial portion of the genetic contribution to sleep apnoea, highlighting the importance of studying symptoms on a subclinical threshold, an approach that has already proven useful at understanding the heterogeneity of other complex traits such as depression and neuroticism. Our study will enable future efforts aimed at understanding the underlying genetic architecture of OSA using multivariate statistical genetic approaches.

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**Fig. 6 Polygenic scores predict snoring and probable apnoea in an independent sample.**

(a) Forest plot showing the odds ratios (and 95% CI) by decile of polygenic score (PGS) for snoring from the UK Biobank discovery sample (relative to the bottom decile = 1) for recent snoring and probable sleep apnoea measured in an independent target sample of ~8000 unrelated Australian adults from the Australian Genetics of Depression Study (AGDS). The x-axis represents the p-value threshold used for variant inclusion during genetic scoring; the y-axis represents the amount of variance explained (change in Nagelkerke R²). The colour of each bar represents the significance of the association between the PGS and recent snoring (−log10 p-value), while the exact p-value (Wald’s test) is shown above each bar.

(b) Variance explained (% of variance calculated from UK Biobank summary statistics. The y-axis represents the amount of variance explained (change in Nagelkerke R²). The colour of each bar represents the significance of the association between the PGS and recent snoring (−log10 p-value), while the exact p-value (Wald’s test) is shown above each bar.

(c) Variance explained (%) of recent snoring in AGDS explained by PGS calculated from UK Biobank discovery sample (relative to the bottom decile = 1) for recent snoring and probable sleep apnoea measured in an independent target sample of ~8000 unrelated Australian adults from the Australian Genetics of Depression Study (AGDS). The x-axis represents the p-value threshold used for variant inclusion during genetic scoring; the y-axis represents the amount of variance explained (change in Nagelkerke R²). The colour of each bar represents the significance of the association between the PGS and recent snoring (−log10 p-value), while the exact p-value (Wald’s test) is shown above each bar.
studies should assess this in a more systematic manner. Our results highlight the importance and utility of studying snoring, and unveil opportunities for understanding highly related sleep traits and disorders, including OSA.

Our initial MR results using GSMR suggested a mutual causal relationship between BMI and snoring, and a similar pattern was observed for heart attack, but only a one-way causal relationship of whole-body fat mass causing snoring. We hypothesized BMI to be more heterogeneous and potentially more pleiotropic than whole-body fat mass. In fact, MR is known to be confounded by pleiotropy. Interestingly, a one-way causal relationship between snoring and pulse rate, which survived adjustment for BMI, was identified. Nonetheless, this association did not reach statistical significance when accounting for sample overlap (i.e., sex-stratified GSMR) or when using other MR methods that also account for pleiotropy. The only causal associations that survived sample overlap and multiple testing correction were BMI or whole-body fat mass causing snoring. Evidence for a causal association was also observed from methods such as IVW-MR and weighted median MR in addition to GSMR. Using more stringent methods such as MR-Egger, the association did not retain statistical significance. Nonetheless, it is known that MR-Egger is a less powered method. Furthermore, the MR-Egger intercept was not significantly different from zero, thus suggesting that the IVW-MR causality estimate is likely to be unbiased. In addition, GSMR removes pleiotropic instruments using a HEIDI outlier filter and should be unbiased by pleiotropy. Overall, we believe this to be a compelling evidence of a causal effect of BMI on snoring, but caution should be taken given the results from MR-Egger and when extrapolating this observation to other related traits such as OSA. The lower number of instruments available for snoring as an exposure (Supplementary Table 2) makes it hard to assess whether the lack of significant results using snoring as an exposure was due to a lack of power or due to a lack of a true causal effects. Future efforts could leverage novel statistical genetics methods that use all the GWAS results to test whether the associations observed could be explained by a causality rather than pleiotropy.

Finally, we assessed the validity of our GWAS results by using genetic scoring on an independent sample of Australian adults with data on recent snoring. Our successful prediction of snoring using PGS supports the external validity of our genetic association results. Remarkably, we predicted probable OSA using a snoring-derived PGS. Thus, investigating the aetiology of snoring could also help uncover the aetiology and genetic architecture of OSA, a task that has proved to be difficult and challenging. Future efforts could assess the utility of snoring-derived PGS as an addition to the current battery of tests used to more accurately diagnose OSA, particularly given the issue of potential OSA underdiagnosis.

Our results highlight the utility of studying snoring and provide important insights into its aetiology and genetic architecture. However, some limitations must be acknowledged. Analyses used self-reported snoring with the item relying on a partner or close friend complaining about the participant’s snoring. Thus, the case definition might be subject to participant-specific recall and subjective biases. Nonetheless, we hypothesize that this limitation might result in the inclusion of some cases as controls (i.e., snoring participants living alone) and therefore bias our results towards the null rather than creating false positives. To avoid confounding due to population stratification, we only included samples of European ancestry in our analyses. This is particularly important, given reports of ethnic differences associated with snoring prevalence. Nonetheless, excluding other populations can limit the generalizability of these results outside the populations studied. As previously discussed, we cannot identify which, if any, sex-specific genetic observations (e.g., differences in SNP heritability) are due to true genetic effects rather than power differences between the samples. Studying the relationship between snoring and craniofacial phenotypes could provide important insights, given that these traits are likely to share a common aetiology. Nonetheless, there is a limited number of available GWAS summary statistics of craniofacial structure phenotypes. Finally, the fact that PGS for snoring predicted less than 1% of the variance on recent snoring suggest that the GWAS is still underpowered. The heritability for snoring in twin studies is estimated in the range of 18–28%, although some of the missing heritability for snoring may come from dominant genetic effects, it is likely that an increased power and studying rare variants yield more powered genetic predictors.

In summary, we provide insights into the aetiology of snoring, its risk factors and genetic underpinnings. Our observational analyses showed a higher prevalence of snoring in males compared with that in females, and effects of age, BMI, SES smoking and alcohol consumption. In addition, tobacco smoking showed a higher effect on snoring prevalence in females compared with that in males, alcohol consumption displayed a higher effect on snoring prevalence in males compared with that in females and SES seemed to be only associated with snoring in males. GWAS identified 127 genome-wide significant associations across 41 genomic risk loci with $h^2_{SNP} = 9.9\%$. We found two loci with differential sex effect sizes, but no evidence for large-scale sex-specific genetic differences. We showed that most of the SNP heritability identified is not simply due to BMI. We also found evidence of a causal relationship from BMI or whole-body fat mass to snoring. Evidence of genetic overlap between snoring and other cardiometabolic, respiratory, neurological and psychiatric traits was found. Finally, we used the GWAS summary statistics to derive individual PGS and predict both recent snoring and probable OSA in an independent sample of Australian adults, thus confirming the relevance of snoring as a sleep-related complex trait. Future studies should aim at leveraging powered GWAS on craniofacial structures, alcohol and tobacco behaviours, to assess whether they are causal of snoring and to assess the amount of shared genetic overlap between OSA and habitual snoring, as the latter may serve to boost the power of obstructive sleep apnoea genetic studies.

Methods
Discovery sample and phenotypic information. Participants included in the present study were of European ancestry from the UK Biobank. Briefly, this resource recruited participants between 2006 and 2010 to assess lifestyle, anthropometric and health-related variables. Participants self-reported on sleep-related traits. Snoring was assessed as a single item (Field-ID: 1210): "Does your partner or a close relative or friend complain about your snoring?" This question could be answered with "Yes", "No", "Don’t know", or "Prefer not to answer". We excluded participants whose answers were "Don’t know" (n = 29,309) or "Prefer not to answer" (n = 6854) from our analyses (Supplementary Table 3 shows the total sample size for each GWAS, including sensitivity and sex-stratified analyses). OSA cases were determined on the basis of either ICD-10 diagnosis code or self-report of sleep apnoea diagnosis in the UK Biobank.

Ethical regulations. The UK Biobank study was approved by the National Health Service National Research Ethics Service (ref. 11/NW/0382) and all participants provided written informed consent to participate in the UK Biobank study. Information about ethics oversight in the UK Biobank can be found at https://www.ukbiobank.ac.uk/ethics/. Regarding the AGDS, all participants provided informed consent prior to participating in the study. This study and all questionsnaires used for AGDS were approved by the QIMR Berghofer Human Research Ethics Committee.

Data extraction and statistical analyses. Raw data were extracted from the UK Biobank under Application Number 25391. For a description of the field codes and instances used, refer to Supplementary Table 4. Data were re-coded to remove missing data and uninformative responses (e.g., “I don’t know” or “I would rather not answer”). Phenotype-derived estimates such as prevalence and associations
between variables were calculated using python. Libraries such as NumPy (https://docs.scipy.org/doc/numpy/user/) and SciPy (https://docs.scipy.org/doc/) were used for descriptive statistics and inference (for the effect allele present in an individual). Finally, the SNP dosage effects were summed across all loci per individual. To assess the association between the PGS and snoring and probable OSA, we employed a logistic regression (python statsmodels). The target sample for snoring was a subset (n = 9026) of the AGDS with data on recent snoring collected through the self-reported item: ‘During the last month, on how many nights or days per week have you had or been told you had loud snoring.’ The item for probable OSA was: ‘During the last month, how on many nights or days per week have you or had been told your breathing stops or you choke or struggle for breath.’ For both items, a positive response was considered one to two times per week up to five or seven times per week and the answer ‘Rarely, less than once a week’ was excluded. Only a subset (n = 8000) of highly unrelated individuals (genetic relatedness < 0.05) were included in the analyses.

**Post-GWAS annotation and functional mapping.** SNP annotation was conducted using the FUMA platform. Risk loci are defined as up to 250 kb based on the most right and left SNPs from each LD block. Gene-based tests were performed using Multi-marker Analysis of GenoMic Annotation (MAGMA) as implemented on the FUMA platform, which provides aggregate association p-values based on all variants located within a gene and its regulatory regions. We used the GWAS summary statistics to conduct a MAGMA analysis in the FUMA platform (https://fuma.ctglab.nl/). This analysis includes a gene-based test to detect significant SNPs associated with snoring. The prioritized genes based on positional and eQTL mapping were further used to perform gene-set enrichment analysis against the traits available in the GWAS catalogue. Furthermore, we used FUMA to perform tissue-enrichment analysis, based on data from the GTEx project (https://gtexportal.org/home/documentationPage).

**Genetic correlation analyses.** We performed genetic correlation analyses to estimate genetic correlations between the discovery, sensitivity and sex-stratified snoring GWAS summary statistics using LD score regression (LDSC) as implemented in the Complex Trait Genomics Virtual Lab (CTG-VL, http://genoma.io). Further, to uncover genetically correlated traits with snoring, genetic correlation analyses using LDSC were performed on the platforms CTG-VL and LDHub (http://ldsc.broadinstitute.org/ldhub/), which aggregate summary statistics for GWAS on hundreds of traits.

**Mendelian randomization.** Mendelian randomization (MR) is a method in which genetic variants (e.g., SNPs) are used as instrumental variables to determine causal effects. Three relevant assumptions must be taken into consideration: (I) genetic variants (e.g., SNPs) are used as instrumental variables to determine causal effects, (II) genetic variants must be associated with the exposure of interest, and (III) genetic variants must be independent of the outcome through other mechanisms. We used GSMR, an approach that leverages the usage of multiple independent variables (SNPs) strongly associated with the outcome, to overcome these assumptions, as implemented in the CTG - VL (http://genoma.io). We used GSMR to assess causal relationships between snoring and BMI, whole-body fat mass and pulse rate using our results and existing summary statistics for these traits. To avoid possible confounding from sample overlap, we performed GSMR using the summary statistics derived from sex-stratified GWAS. For example, the female snoring GWAS results were used as exposure, whereas the male pulse rate GWAS results were used for the outcome. Finally, sensitivity two-sample MR analyses (MR-Egger, median-weighted estimator, IVW-MR and weighted mode) were performed using the R library MRBase and UK Biobank sex-stratified summary statistics to ensure non-overlapping samples.

**Target sample and polygenic scoring.** To quantify for the cumulative genetic associations for snoring, we calculated PGS using a clumping + thresholding approach. Study description and sample characteristics of the AGDS are available elsewhere. Genotyping was conducted using the Illumina Infinium Global Screening Array platform and genotype imputation using the HaploType Reference Consortium’s reference panel in the Michigan Imputation Server. We carried out after performing standard QC procedures. Briefly, for PGS estimation, we excluded indel, strand ambiguous- and low (R^2 ≤ 0.6) imputation quality variants. The most significant SNPs were selected using a conservative clumping procedure (PLINK1.96; p^2 = 1, 1 = 2^2, q2 = 0.1, kbd = 10000) to correct for inflation arising from LD. Eight PGS were calculated using different p-value thresholds (p < 5 × 10^-8, p < 1 × 10^-5, p < 0.001, p < 0.01, p < 0.05, p < 0.1, p < 0.5, p < 1) as a criteria for SNP inclusion on the PGS calculation. PGS were calculated by multiplying the effect size of a given SNP by the imputed number of copies (using dosage probability of the effect allele present in an individual). Finally, the SNP dosage effects were summed across all loci per individual. To assess the association between the PGS and snoring and probable OSA, we employed a logistic regression (python statsmodels). The target sample for snoring was a subset (n = 9026) of the AGDS with data on recent snoring collected through the self-reported item: ‘During the last month, on how many nights or days per week have you had or been told you had loud snoring.’ The item for probable OSA was: ‘During the last month, how on many nights or days per week have you or had been told your breathing stops or you choke or struggle for breath.’ For both items, a positive response was considered one to two times per week up to five or seven times per week and the answer ‘Rarely, less than once a week’ was excluded. Only a subset (n = 8000) of highly unrelated individuals (genetic relatedness < 0.05) were included in the analyses.

**Reporting summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this article.

**Data availability**

The full GWAS summary statistics for this study will be available through the NHGRI EBI GWAS Catalogue (https://www.ebi.ac.uk/gwas/downloads/summary-statistics). Individual level data for UK Biobank participants are available to eligible researchers through the UK Biobank (www.biobank.ac.uk). Individual level AGDS data can be made available to academic collaborators with an appropriate Data Transfer Agreement. Collaboration proposals can be directed to Professor Nick Martin (nick.martin@qimrberghofer.edu.au).

**Code availability**

Code used as part of the work presented in this manuscript is available from the authors upon reasonable request.

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Author contributions

M.E.R. and G.C.-P. conceived and directed the study. A.I.C. and L.M.G.-M. performed most of the statistical and bioinformatics analyses, with support from G.C.-P. and M.E.R. E.M.B. and N.G.M. collected and contributed data from the Australian sample. A.I.C., L.M.G.-M., M.E.R. and G.C.-P. wrote the paper with feedback from all co-authors.

Competing interests

The authors declare no competing interests.

Additional information

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