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Surgical removal of tonsils and risk of COVID-19: a nested case–control study using data from UK Biobank and AMORIS Cohort

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Abstract

Background To investigate the association between surgical removal of tonsils and risk of COVID-19 with different severity.

Methods Through a nested case–control study during January 31st to December 31st 2020, including 58,888 participants of the UK Biobank, we investigated the association of tonsillectomy with the future risk of mild and severe COVID-19, using binomial logistic regression. We further examined the associations of such surgery with blood inflammatory, lipid and metabolic biomarkers to understand potential mechanisms. Finally, we replicated the analysis of severe COVID-19 in the Swedish AMORIS Cohort ($n = 451{,}960$).

Results Tonsillectomy was associated with a lower risk of mild (odds ratio [95% confidence interval]: 0.80 [0.75–0.86]) and severe (0.87 [0.77–0.98]) COVID-19 in the UK Biobank. The associations did not differ substantially by sex, age, Townsend deprivation index, or polygenic risk score for critically ill COVID-19. Levels of blood inflammatory, lipid and metabolic biomarkers did, however, not differ greatly by history of surgical removal of tonsils. An inverse association between tonsillectomy and severe COVID-19 was also observed in the AMORIS Cohort, primarily among older individuals (> 70 years) and those with ≤ 12 years of education.

Conclusions Surgical removal of tonsils may be associated with a lower risk of COVID-19. This association is unlikely attributed to alterations in common blood inflammatory, lipid and metabolic biomarkers.

Keywords Tonsillectomy, COVID-19, Risk factor, SARS-CoV-2, UK Biobank, AMORIS Cohort

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Background

The World Health Organization declared an end of the COVID-19 pandemic as a global health emergency in May 2023; however, globally, millions of people continue to be infected with SARS-CoV-2, and thousands of people continue to die from the disease each week [1]. The identification of individuals at high risk of COVID-19, especially severe cases, therefore, remains crucial.

The palatine tonsils are secondary lymphoid organs at the mucosal surface of the oropharynx and nasopharynx, playing an important role in infections of the upper respiratory tract [2]. Tonsils are immunologically active in childhood and atrophy with age. Tonsillectomy is the most common otorhinolaryngological surgery, mainly performed to treat tonsillar inflammation or obstructive sleep apnea [3, 4]. Given the role of tonsils in respiratory infections, a potential link has been proposed between previous tonsillectomy and susceptibility to COVID-19 infection and severity. Three studies have so far examined COVID-19 in relation to tonsillectomy [5–7]. One study showed that individuals with tonsillectomy had a lower-than-expected rate of SARS-CoV-2 test positivity, whereas no association was observed between tonsillectomy and disease severity [5]. Another study showed that, among people with a positive COVID-19 test, individuals with tonsillectomy had a higher burden of some symptoms, but not others, as well as a similar risk of hospitalization compared to those without tonsillectomy [6]. The third study showed that, among patients with chronic tonsillitis, chronic adenoiditis, or peritonsillar abscess, an inverse association was noted between tonsillectomy and COVID-19, as well as mortality, although the former was not statistically significant [7].

As the existing studies are either relatively small or focused on individuals with confirmed diagnosis of COVID-19 or clinical indications for tonsillectomy, we examined the association of tonsillectomy with the subsequent risk of COVID-19 with different severity in the general population, using prospectively collected data from the UK Biobank and the Swedish Apolipoprotein-Related Mortality Risk (AMORIS) Cohort. In addition, we investigated potential effect modifiers (i.e., sex, age, socioeconomic status, and genetic risk score for critically ill COVID-19) and mediators (e.g., blood inflammatory, lipid and metabolic biomarkers) for the association.

Methods

Study materials

UK Biobank is a cohort with half a million participants recruited during 2006–2010 [8], including information on socio-demographic factors and lifestyle collected at baseline as well as various health outcomes collected through periodic linkages to multiple registers [9, 10]. AMORIS is a population-based cohort, including 806,328 individuals undergoing health examinations during 1985–1996 in Stockholm mainly who were followed through linkages to different population and health registers individually, using the unique Swedish personal identity numbers [11]. Based on the dates of first COVID-19 diagnosis (January 31st, 2020, in the UK and January 30th, 2020, in Sweden) and the start dates of COVID-19 vaccination (December 8th, 2020, in the UK and December 27th, 2020, in Sweden), we determined the study period as from January 31st to December 31st, 2020, to study the association of tonsillectomy with the risk of COVID-19 in an unvaccinated population.

Study design

Among the 502,384 participants of the UK Biobank, 59,907 had at least one SARS-CoV-2 PCR test, either positive or negative, during the study period, according to data from England, Scotland, and Wales. After excluding participants who withdrew or had conflicting information, participants with adenoidectomy alone before study start or a surgical removal of tonsils or adenoids after study start, as well as participants with a hospitalization record where COVID-19 was listed as a secondary diagnosis (i.e., we could not define the severity of COVID-19 for these individuals), we included 58,888 individuals in the analysis (Additional file 1: Fig. S1). These individuals were classified into three groups, namely cases of severe COVID-19, cases of mild COVID-19, and controls. Severe COVID-19 was ascertained through a hospitalization (including ICU admission) with COVID-19 as the main discharge diagnosis or death due to COIVD-19, identified through inpatient care data and cause of death data, using the 10th International Classification of Diseases (ICD) codes U07.1 and U07.2. Mild COVID-19 was defined through a positive SARS-CoV-2 PCR test without inpatient care or death due to COVID-19. The rest of individuals who tested for COVID-19 but with no positive finding were defined as controls.

Among the 806,328 participants of AMORIS, 533,113 were still alive on January 30th, 2020 (Additional file 1: Fig. S2). As the UK Biobank participants were at least 50 years during the study period, we focused the analysis of AMORIS on individuals at 50 or above as well. We excluded participants with adenoidectomy alone before study start or a surgical removal of tonsils or adenoids after study start, leaving 451,960 individuals in the analysis. These individuals were classified into two groups, namely cases of severe COVID-19 and controls. Severe COVID-19 was ascertained through a hospitalization with COVID-19 as the main discharge diagnosis, an ICU admission for COVID-19, or death due to COIVD-19, identified via the Swedish Patient, the Intensive Care, and

the Causes of Death Registers, respectively, using ICD codes U07.1 and U07.2. In Sweden, the Patient Register has collected data on inpatient care since 1964 [12], the Intensive Care Register has collected data on ICU care since 2008 [13], whereas the Causes of Death Register has registered underlying and contributory causes for all deaths since 1961 [14]. The rest of the participants were defined as controls, i.e., individuals without severe COVID-19.

Surgical removal of tonsils

A surgical removal of tonsils, either tonsillectomy or adenotonsillectomy, before study start was used as the exposure of interest. In the UK Biobank, this was ascertained from the hospital inpatient records, the general practitioner (GP) clinical event records, and baseline questionnaires (i.e., self-reported operation) (Additional file 1: Table S1). In AMORIS, we identified such procedure before study start from the Patient Register. The Patient Register covers all inpatient care in Stockholm since 1972 [12] as well as > 80% of specialized outpatient care in Sweden since 2001. As tonsillectomy was exclusively performed in inpatient care until 2006 in Sweden [15], we identified it from both inpatient and outpatient care. All codes used in the UK Biobank and AMORIS are shown in Additional file 1: Table S2.

Covariates

Given the availability of information, we used different sets of covariates in the analysis of the two data sources. In the UK Biobank, we included sex, age, educational attainment, ethnicity, Townsend deprivation index (TDI), body mass index (BMI), smoking status, and overall health rating as covariates. TDI, including information on employment status, car and home ownership, and household overcrowding, calculated for each output area from the UK national census, was used to approximate the socioeconomic status of the UK Biobank participants. At the baseline assessment, the participants were assigned a TDI score based on their residential postal codes and the latest national census data. Overall health rating was assessed by the question "In general how would you rate your overall health?" at the baseline assessment, including response options "excellent", "good", "fair", "poor", "do not know", and "prefer not to answer". Furthermore, using the genotyping data of the UK Biobank, we calculated polygenic risk scores (PRSs) for critically ill COVID-19, as an effect modifier, to estimate the impact of individual genetic predisposition to severe COVID-19 on the studied association. We hypothesized that the association of tonsillectomy with risk of COVID-19 might vary between individuals with a high versus a low genetic predisposition to severe COVID-19. Detailed information on the calculation of PRSs is shown in Additional file 1: Supplementary Methods. After the exclusion of 3460 non-white individuals, 43,604 individuals with data on PRSs were included in this analysis. In AMORIS, we included sex, age, educational attainment, country of birth, employment status, and level of income as covariates. There were different degrees of missing data in covariates studied in the UK Biobank and AMORIS, we treated individuals with missing or unknown data on a covariate as a separate group.

Blood inflammatory, lipid, and metabolic biomarkers

To understand the potential causal pathways between surgical removal of tonsils and COVID-19, we analyzed data on blood inflammatory (e.g., leukocytes), lipid, and metabolic biomarkers (e.g., triglycerides and glucose) in the UK Biobank. The inflammatory biomarkers were measured through hematological assays of whole blood while lipid and metabolic biomarkers were measured using Beckman Coulter AU5900 Platform. All biomarker measurements were taken from blood samples collected at recruitment to the UK Biobank and analyzed at UK Biobank central laboratory within 24 h of blood draw. In addition to these, we calculated lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII; [neutrophil × platelet]/lymphocyte) as additional biomarkers. In this analysis, we used the entire UK Biobank population with information on these biomarkers as the study sample and used surgical removal of tonsils before recruitment to the UK Biobank as the exposure.

Statistical analyses

In the UK Biobank, we used binomial logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of mild or severe COVID-19 in relation to surgical removal of tonsils. We conducted an unadjusted model (Model 1) and a multivariable model adjusted for sex, age, educational attainment, ethnicity, TDI, BMI, smoking status, and overall health rating (Model 2). As inpatient care data for participants from Wales was only available until February 28th, 2018, we repeated the main analysis by excluding individuals registered in Wales. We also performed a sensitivity analysis by additionally adjusting for hypertension and diabetes in Model 2 to assess the potential influence of such comorbidities. To assess potential effect modification, we performed stratified analyses by sex, age, TDI, and PRS for critically ill COVID-19. To quantify differences between group specific ORs, we added interaction terms (i.e., exposure*effect modifier) to the logistic regression. Furthermore, to assess potential difference between a

surgical removal of tonsils in childhood and later, we performed subgroup analysis by age at surgery. Finally, we analyzed the associations for inflammatory, lipid, and metabolic biomarkers in relation to tonsillectomy using linear regression adjusted for sex, ethnicity, age, and BMI at blood sampling. We then performed mediation analyses after additional adjustment for these biomarkers in model 2 to assess their contribution to the association between surgical removal of tonsils and COVID-19. As only a small number of participants had undergone adenotonsillectomy, we focused the stratified analysis, the subgroup analysis by age at surgery, and the mediation analysis on tonsillectomy.

In AMORIS, we used logistic regression to estimate OR and 95%CI of severe COVID-19. Given the similar results noted for tonsillectomy and adenotonsillectomy in the UK Biobank, we combined these two procedures in this analysis to improve statistical efficiency. In the multivariable model, we adjusted for sex, age, educational attainment, country of birth, employment status, and level of income. We performed two sensitivity analyses. First, we additionally adjusted for hypertension and diabetes to assess the potential influence of such comorbidities. Second, as we restricted the analysis to people at age 50 or above, we performed another sensitivity analysis without such restriction to assess whether the result would differ after including also younger individuals.

Analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 4.2.2.

Results

There were 9074 cases of mild COVID-19 and 2130 cases of severe COVID-19 in the analysis of the UK Biobank (Table 1). Compared to controls, cases of severe COVID-19 were older, more likely male, and had a higher TDI and a poorer overall health rating. No clear difference was noted between cases of mild COVID-19 and controls.

After multivariable adjustment, tonsillectomy was associated with a lower risk of mild COVID-19 (OR 0.80; 95%CI 0.75–0.86) but no association was noted for adenotonsillectomy (Table 2). Tonsillectomy (OR 0.87; 95%CI 0.77–0.98) and adenotonsillectomy (OR 0.66; 95%CI 0.47–0.90) were both associated with a lower risk of severe COVID-19. There was no change in the results after excluding participants registered in Wales (Additional file 1: Table S3) or with the additional adjustment for hypertension and diabetes (Additional file 1: Table S4).

Similar associations for mild and severe COVID-19 were noted for male and female, younger and older, individuals with higher or lower TDI, as well as people with higher or lower PRS for critically ill COVID-19 (all p for difference > 0.05; Additional file 1: Table S5). Most of the cases (mild 62.5%, severe 71.7%) and controls (71.1%) with tonsillectomy had the surgery performed at age 18 or earlier. Although we observed a slightly stronger association for tonsillectomy performed at age 18 or earlier (OR 0.79; 95%CI 0.73–0.85 for mild COVID-19; OR 0.85; 95%CI 0.75–0.97 for severe COVID-19), compared to tonsillectomy after 18, the difference was not statistically significant (P for difference = 0.383 and 0.194, respectively) (Additional file 1: Table S6).

We observed only weak associations of tonsillectomy with lymphocytes, neutrophils, NLR, PLR, SII, albumin, glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and Apolipoprotein B (ApoB) (Table 3). These associations were largely similar regardless of age at surgery. The associations of tonsillectomy with COVID-19 did not change after additionally adjusting for these biomarkers, either (Additional file 1: Table S7).

There were 5127 cases of severe COVID-19 and 446,833 controls in the analysis of AMORIS (Additional file 1: Table S8). Cases of severe COVID-19 were older, more likely male, less likely born in Sweden, and more likely unemployed, had fewer years of education and lower levels of income, than controls. Tonsillectomy or adenotonsillectomy was associated with a lower risk of severe COVID-19 (OR 0.55; 95%CI 0.44–0.70) in the unadjusted model; this association, however, diminished after multivariable adjustment (OR 0.88; 95%CI 0.70–1.11) (Table 4). The association remained similar after additionally adjusting for hypertension and diabetes or without age restriction (Additional file 1: Table S4). The multivariable-adjusted association was mainly attributed to individuals above 70 (OR 0.67; 95%CI 0.48–0.94) and those with 12 or less years of education (OR 0.75; 95%CI 0.56–1.01) (Additional file 1: Table S9).

Discussion

The analysis of UK Biobank data showed that individuals with a history of tonsillectomy exhibited a lower risk of both mild and severe COVID-19 compared to those without such exposure. This inverse association was consistently observed across different groups based on sex, age, socioeconomic status, and genetic risk for critically ill COVID-19. The association was unlikely to be attributed to blood inflammatory, lipid, or metabolic biomarkers investigated in the study. A similar odds ratio for severe COVID-19 was obtained in the Swedish AMORIS Cohort, although statistically significant results were only observed among older individuals and those with a lower level of education.

Tonsils are part of the immune system and help protect the body from infectious diseases like bacterial and viral infections, especially during childhood. Although

Table 1 Characteristics of the study participants by COVID-19 status—an analysis of the UK Biobank

Characteristics	No COVID-19 (*N* = 47,684)	Mild COVID-19 (*N* = 9074)	Severe COVID-19 (*N* = 2130)	All (*N* = 58,888)
Sex, *N* (%)				
Female	25,896 (54.3%)	4986 (54.9%)	812 (38.1%)	31,694 (53.8%)
Male	21,788 (45.7%)	4088 (45.1%)	1318 (61.9%)	27,194 (46.2%)
Age				
Mean (SD)	69.1 (8.1)	63.8 (8.3)	71.5 (7.8)	68.4 (8.4)
Range	50.0–83.7	50.0–83.2	50.2–83.4	50.0–83.7
Educational attainment, *N* (%)				
No college	32,379 (67.9%)	6540 (72.1%)	1633 (76.7%)	40,552 (68.9%)
College	14,237 (29.9%)	2359 (26.0%)	421 (19.8%)	17,017 (28.9%)
Unknown	1068 (2.2%)	175 (1.9%)	76 (3.6%)	1319 (2.2%)
Ethnicity, *N* (%)				
White	44,984 (94.3%)	8242 (90.8%)	1892 (88.8%)	55,118 (93.6%)
Non-white	2449 (5.1%)	795 (8.8%)	216 (10.1%)	3460 (5.9%)
Unknown	251 (0.5%)	37 (0.4%)	22 (1.0%)	310 (0.5%)
Townsend deprivation index, *N* (%)				
Low	23,074 (48.4%)	4001 (44.1%)	762 (35.8%)	27,837 (47.3%)
High	24,534 (51.5%)	5059 (55.8%)	1367 (64.2%)	30,960 (52.6%)
Unknown	76 (0.2%)	14 (0.2%)	<5	91 (0.2%)
Body mass index, *N* (%)				
Normal or underweight	13,979 (29.3%)	2625 (28.9%)	357 (16.8%)	16,961 (28.8%)
Overweight	20,008 (42.0%)	3808 (42.0%)	867 (40.7%)	24,683 (41.9%)
Obese	13,343 (28.0%)	2591 (28.6%)	869 (40.8%)	16,803 (28.5%)
Unknown	354 (0.7%)	50 (0.6%)	37 (1.7%)	441 (0.7%)
Smoking status, *N* (%)				
Never	24,341 (51.0%)	4949 (54.5%)	858 (40.3%)	30,148 (51.2%)
Former	17,616 (36.9%)	3108 (34.3%)	950 (44.6%)	21,674 (36.8%)
Current	5371 (11.3%)	982 (10.8%)	292 (13.7%)	6645 (11.3%)
Unknown	356 (0.7%)	35 (0.4%)	30 (1.4%)	421 (0.7%)
Overall health rating, N (%)				
Good	32,447 (68.0%)	6547 (72.2%)	1102 (51.7%)	40,096 (68.1%)
Fair	11,732 (24.6%)	2062 (22.7%)	706 (33.1%)	14,500 (24.6%)
Poor	3151 (6.6%)	402 (4.4%)	290 (13.6%)	3843 (6.5%)
Unknown	354 (0.7%)	63 (0.7%)	32 (1.5%)	449 (0.8%)
Surgical removal of tonsils, *N* (%)				
No	36,910 (77.4%)	7440 (82.0%)	1734 (81.4%)	46,084 (78.3%)
Tonsillectomy	9252 (19.4%)	1302 (14.3%)	356 (16.7%)	10,910 (18.5%)
Adenotonsillectomy	1522 (3.2%)	332 (3.7%)	40 (1.9%)	1894 (3.2%)

SD standard deviation

a removal of tonsils has not been shown to leave a substantial impact on the immune functions, either humoral or cellular [16, 17], several studies have suggested that a surgical removal of tonsils may be associated with the risk of various diseases later in life, including acute myocardial infarction [18], periodontitis [19], and cancer [20]. The few studies on respiratory infections have rendered largely inconsistent results. A Danish study found tonsillectomy to be associated with increased long-term risk of respiratory and infectious diseases [21], whereas two Asian studies reported null or inverse associations between tonsillectomy and risk of hospital visit for acute respiratory infection [22, 23]. To our knowledge, only three studies have, to date, examined the role of tonsillectomy on COVID-19-related outcomes [5–7]. Although these previous studies are supportive of our findings, i.e., tonsillectomy is associated with a lower risk of COVID-19, regardless of

Table 2 Odds ratio (OR) and 95% confidence interval (CI) of mild or severe COVID-19 in relation to surgical removal of tonsils—an analysis of the UK Biobank

Surgical removal of tonsils	Mild COVID-19 OR (95%CI)			Severe COVID-19 OR (95%CI)		
	Cases/Controls	Model 1[a]	Model 2[b]	Cases/Controls	Model 1[a]	Model 2[b]
No	7440/36,910	Ref	Ref	1734/36,910	Ref	Ref
Tonsillectomy	1302/9252	0.70 (0.66–0.74)	0.80 (0.75–0.86)	356/9252	0.82 (0.73–0.92)	0.87 (0.77–0.98)
Adenotonsillectomy	332/1522	1.08 (0.96–1.22)	1.01 (0.89–1.14)	40/1522	0.56 (0.40–0.76)	0.66 (0.47–0.90)

[a] Mode 1: not adjusted for any covariate

[b] Mode 2: adjusted for age, sex, educational attainment, ethnicity, Townsend deprivation index, body mass index, smoking status, and overall health rating

disease severity, it is difficult to directly compare findings between these studies. For instance, the present study utilized two data sources of population cohorts with a large sample size and prospectively collected information on tonsillectomy and COVID-19, whereas the previous studies had either a relatively small sample size or focused on specific patient groups (i.e., individuals with confirmed COVID-19 or a clinical diagnosis indicative of tonsillectomy). Nevertheless, our study additionally showed consistent results between men and women, older and younger individuals, people with higher or lower socioeconomic status, as well as individuals with different genetic predisposition to severe COVID-19, suggesting a potentially universal protection of tonsillectomy against COVID-19.

To understand the pathways underlying the observed lower risk of COVID-19 in relation to tonsillectomy (and adenotonsillectomy), we examined the role of such operation on levels of blood inflammatory biomarkers. Although we observed some associations of tonsillectomy with lymphocytes, neutrophils, NLR, PLR, SII, and albumin, the magnitude of these associations is small and unlikely clinically significant. Further, as cardiometabolic diseases have been shown as risk factors for COVID-19, especially severe COVID-19 [24], we examined the link between surgical removal of tonsils and lipid and metabolic biomarkers. Similarly, although tonsillectomy was associated with a slightly higher level of TC, LDL-C, and ApoB as well as a lower level of glucose, the associations were weak in general. Regardless, additionally adjusting for these biomarkers did not change the association between removal of tonsils and COVID-19. Taken together, these results suggest that the association of tonsillectomy with COVID-19 is unlikely greatly attributed to altered peripheral immunity or lipid/glucose metabolism.

More research is needed to investigate other mechanisms, such as coronavirus colonization and enzymic or immune activities of the palatine tonsil tissue. For instance, ACE2 and TMPRSS family members, including TMPRSS2 and TMPRSS4, are known host entry factors of SARS-CoV-2 [25], whereas ACE2 and TMPRSS2 expression has been reported in the suprabasal layers of palatine tonsils and tonsillar crypt [26] as well as the squamous epithelium lining oropharyngeal tonsillar tissue [27]. Tonsillectomy might therefore result in a reduction in host entry factors for SARS-CoV-2. Further, SARS-CoV-2 is primarily inhaled through the oral and nasal cavity, subsequently causing respiratory symptoms in the lower respiratory tract. Waldeyer's ring may therefore play an important role in the transmission of viruses from upper to lower respiratory tract. For instance, tonsils could serve as a reservoir for SARS-CoV-2, facilitating the spread of the virus [28]. Finally, it is also possible that people with tonsillectomy have had more experience with different coronaviruses, which are the frequent causes for upper respiratory infections, both before (e.g., repeated tonsillitis is a common indication of tonsillectomy) and after the surgical removal [21], providing potentially a cross-immunity against COVID-19 [29] that lasts for a long time [30]. On the other hand, sleep apnea has been found to be associated with an increased risk of severe COVID-19 [31, 32], while tonsillectomy recommended for individuals with sleep apnea in childhood [33] may to some extent protect them from COVID-19, particularly the severe form of COVID-19. Regardless, a better understanding of the biological underpinning of the noted association between tonsillectomy and COVID-19 might help in understanding the COVID-19 pandemic as well as similar pandemics in the future.

Our study has several strengths. First, it is the largest to date to examine the link between tonsillectomy and COVID-19 of different severity as well as the first one using prospectively and independently collected information on exposure and outcome, greatly alleviating concerns on systematic errors like information and selection biases. The universal, equally accessible health

Table 3 Association between a surgical removal of tonsils and levels of blood inflammatory, lipid and metabolic biomarkers—an analysis of the UK Biobank[a]

Inflammatory, lipid, or metabolic biomarkers (unit, *N*)	No surgery	Tonsillectomy		Age at tonsillectomy, years			
				<18		>18	
	Mean (SD)	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)
Inflammatory biomarkers							
Leukocytes (10^9/l, 478,052)	6.88 (2.14)	6.91 (2.07)	0.005 (−0.010–0.021)	6.89 (1.99)	−0.010 (−0.027–0.007)	7.01 (2.45)	0.092 (0.054–0.129)
Lymphocytes (10^9/l, 477,168)	1.96 (1.17)	1.98 (1.2)	0.017 (0.008–0.026)	1.97 (1.09)	0.008 (−0.001–0.018)	2.05 (1.68)	0.064 (0.043–0.085)
Neutrophils (10^9/l, 477,168)	4.23 (1.43)	4.23 (1.4)	−0.015 (−0.025 to −0.004)	4.23 (1.4)	−0.021 (−0.032 to −0.009)	4.27 (1.43)	0.018 (−0.007–0.043)
Monocytes (10^9/l, 477,168)	0.48 (0.28)	0.48 (0.23)	0.001 (0–0.003)	0.48 (0.23)	0 (−0.002–0.003)	0.48 (0.25)	0.007 (0.002–0.012)
Platelet (10^9/l, 478,054)	252.89 (60.16)	253.79 (60.04)	0.302 (−0.135–0.738)	253.12 (60.04)	0.155 (−0.313–0.623)	257.57 (59.87)	1.102 (0.071–2.133)
CRP (mg/l, 468,457)	2.59 (4.35)	2.65 (4.42)	−0.028 (−0.059–0.004)	2.64 (4.44)	−0.025 (−0.059–0.009)	2.74 (4.32)	−0.043 (−0.118–0.032)
LMR (477,018)[b]	2.07 (0.61)	2.06 (0.6)	0.005 (0–0.009)	2.05 (0.6)	0.003 (−0.002–0.008)	2.11 (0.6)	0.015 (0.005–0.025)
NLR (477,158)[b]	1.11 (0.6)	1.1 (0.59)	−0.017 (−0.022 to −0.013)	1.11 (0.59)	−0.015 (−0.020 to −0.010)	1.07 (0.6)	−0.028 (−0.039 to −0.018)
PLR (477,157)[b]	7.05 (0.54)	7.04 (0.54)	−0.011 (−0.015 to −0.007)	7.05 (0.53)	−0.008 (−0.012 to −0.004)	7.03 (0.54)	−0.027 (−0.037 to −0.018)
SII (477,154)b	9.05 (0.71)	9.05 (0.7)	−0.015 (−0.020 to −0.009)	9.05 (0.7)	−0.014 (−0.020 to −0.008)	9.04 (0.7)	−0.020 (−0.033 to −0.008)
Albumin (g/l, 429,975)	45.2 (2.63)	45.23 (2.6)	0.116 (0.096–0.136)	45.23 (2.6)	0.106 (0.084–0.127)	45.25 (2.58)	0.174 (0.126–0.221)
Lipid and metabolic biomarkers							
Glucose (mmol/l, 429,467)	5.13 (1.25)	5.12 (1.23)	−0.027 (−0.036 to −0.017)	5.12 (1.23)	−0.028 (−0.039 to −0.018)	5.12 (1.22)	−0.018 (−0.041–0.005)
TC (mmol/l, 469,478)	5.68 (1.15)	5.74 (1.15)	0.023 (0.014–0.031)	5.74 (1.14)	0.025 (0.015–0.034)	5.74 (1.16)	0.011 (−0.009–0.031)
LDL-C (mmol/l, 468,595)	3.55 (0.87)	3.59 (0.87)	0.019 (0.012–0.025)	3.59 (0.87)	0.022 (0.015–0.029)	3.58 (0.88)	0.003 (−0.013–0.018)
HDL-C (mmol/l, 429,771)	1.45 (0.38)	1.46 (0.39)	0.002 (0–0.005)	1.46 (0.39)	0.002 (0–0.005)	1.47 (0.39)	0.001 (−0.005–0.007)
TG (mmol/l, 469,103)	1.75 (1.03)	1.75 (1.01)	0 (0–0.008)	1.75 (1)	−0.003 (−0.011–0.005)	1.76 (1.04)	0.021 (0.003–0.038)
ApoA (g/l, 427,410)	1.53 (0.27)	1.55 (0.27)	0.002 (0–0.004)	1.55 (0.27)	0.003 (0–0.005)	1.55 (0.28)	0.002 (−0.002–0.007)
ApoB (g/l, 467,097)	1.03 (0.24)	1.04 (0.24)	0.004 (0.003–0.006)	1.04 (0.24)	0.005 (0.003–0.007)	1.04 (0.24)	0.002 (−0.003–0.006)
LpA (mmol/l, 375,543)	44.78 (49.23)	44.3 (49.18)	−0.168 (−0.584–0.248)	44.3 (49.22)	−0.100 (−0.545–0.345)	44.32 (48.97)	−0.548 (−1.527–0.431)

CRP C-reactive protein, *LMR* lymphocyte-to-monocyte ratio, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *SII* systemic immune-inflammation index, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *ApoA* apolipoprotein A, *ApoB* apolipoprotein B, *SD* standard deviation, *CI* confidence interval

[a] Linear regression model after adjustment for sex, ethnicity, age, and body mass index at sampling

[b] log2 transformation

care and the mandatory registration of health records in the UK and Sweden starting decades ago could, on the other hand, minimize misclassification bias to the most extent. Finally, we validated some of the findings in two different cohorts, supporting the validity of our main conclusion.

Table 4 Odds ratio and 95% confidence interval of severe COVID-19 in relation to surgical removal of tonsils—analysis of the Swedish AMORIS Cohort

Surgical removal of tonsils	Cases/Controls	Model 1[a]	Model 2[b]
No	5052/435,155	Ref	Ref
Tonsillectomy or adenotonsillectomy	75/11,678	0.55 (0.44–0.70)	0.88 (0.70–1.11)

[a] Model 1: not adjusted for any covariate

[b] Model 2: adjusted for sex, age, country of birth, years of education, employment status, and income

There are also limitations in the study. First, we ascertained tonsillectomy from healthcare and self-report data in the UK Biobank but only from hospital records (since 1970) in AMORIS. Consequently, we missed a large proportion of AMORIS participants exposed to this procedure in early life when hospital records were not available, because most of the participants were in middle and old age during the enrollment period (1985–1996). Although this misclassification is unlikely related to COVID-19 (i.e., non-differential), it dilutes the real association toward null. Second, in the UK Biobank, we identified a population with at least one test for COVID-19 and classified them as with severe, mild, or no COVID-19. Several problems might arise in such a definition. For instance, as systematic serologic testing was not available for all UK Biobank participants during the study period, participants with at least one test for COVID-19 might differ from others in terms of occupation (e.g., more healthcare workers), prevalence of respiratory symptoms, etc. Further, asymptomatic cases of COVID-19 might have been underrepresented in the study population, if they did not receive a test, and it is not clear whether such misclassification is dependent on other factors (e.g., socioeconomic status). In contrast, in AMORIS, we could only identify individuals with or without severe COVID-19. Including individuals with mild COVID-19 as controls had probably also biased the result toward null in AMORIS. Third, we did not have information on the indication and effectiveness of the surgery in either the UK Biobank or AMORIS. It would, however, be interesting to examine whether the observed association between tonsillectomy and COVID-19 could be attributed to the surgery with a specific indication (e.g., tonsil-related conditions) or differ by the effectiveness of the surgery in future studies with access to such information. Finally, our findings are only applicable to an unvaccinated population and to the original strains of the SARS-CoV-2. Whether similar findings will be obtained during later phases of the pandemic and among individuals vaccinated for COVID-19 remains to be studied.

Conclusions

Surgical removal of tonsils, either alone or in conjunction with the removal of adenoids, was associated with a lower risk of both mild and severe COVID-19. This association is unlikely to be attributed to common blood inflammatory or lipid and metabolic biomarkers.

Abbreviations

AMORIS	Apolipoprotein-Related Mortality Risk
BMI	Body mass index
CI	Confidence intervals
CRP	C-reactive protein
GP	General practitioner
HR	Hazard ratio
ICD	International Classification of Disease
LDL-C	Low-density lipoprotein cholesterol
OR	Odds ratios
PRS	Polygenic risk scores
TC	Total cholesterol
TDI	Townsend deprivation index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03587-6.

Additional file 1: Supplementary Methods. Polygenic risk scores (PRSs) for critically ill COVID-19. Table S1. Data sources and the coverage of data used in the UK Biobank and the Swedish AMORIS Cohort. Table S2. Codes used to identify surgical removals of tonsils or adenoids in the UK Biobank and the Swedish AMORIS Cohort. Table S3. Associations of surgical removal of tonsils with the risk of mild or severe COVID-19 – an analysis of the UK Biobank after excluding residents of Wales. Table S4. Associations of surgical removal of tonsils with the risk of COVID-19 after additional adjustment for hypertension and diabetes in the UK Biobank and the Swedish AMORIS cohort as well as without age restriction in the Swedish AMORIS cohort. Table S5. Odds ratio (OR) and 95% confidence interval (CI) of mild or severe COVID-19 in relation to tonsillectomy—stratified analysis of the UK Biobank data by sex, age, Townsend deprivation index (TDI), and polygenic risk score (PRS) for critically ill COVID-19. Table S6. Associations of tonsillectomy with the risk of mild or severe COVID-19 – analysis of the UK Biobank data by age at surgery. Table S7. Associations of tonsillectomy with the risk of mild or severe COVID-19 – analysis of the UK Biobank data with additional adjustment for inflammatory or lipid biomarkers. Table S8. Characteristics of study participants by COVID-19 status – an analysis of the Swedish AMORIS Cohort. Table S9. Associations of surgical removal of tonsils with the risk of severe COVID-19—stratified analyses of the Swedish AMORIS cohort by sex, age, and years of education. Fig. S1. Flowchart of study participants in the analysis of the UK Biobank. Fig. S2. Flowchart of study participants in the analysis of the Swedish AMORIS Cohort.

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Authors' contributions

Y.Y.: formal analysis, investigation, methodology, writing of the original draft. K.H.: data curation, investigation, methodology, validation, review and editing of the manuscript. K.M.: investigation, methodology, review and editing of the

manuscript. M.F.: resources, review and editing of the manuscript. I.J.: conceptualization, review and editing of the manuscript. N.H.: resources, review and editing of the manuscript. F.F.: conceptualization, funding acquisition, review and editing of the manuscript. Z.Z.: conceptualization, funding acquisition, project administration, supervision, review and editing of the manuscript. D.W.: methodology, formal analysis, validation, supervision, review and editing of the manuscript. All authors read and approved the final manuscript.

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Data availability
Data from the UK Biobank (https://www.ukbiobank.ac.uk/) are available to all researchers through application. Data from the AMORIS cohort are not publicly available due to EU and Swedish regulations. Please contact the Steering Group for AMORIS Cohort for more information and potential collaborations (https://ki.se/en/imm/amoris).

Declarations

Ethics approval and consent to participate
The studies of UK Biobank (DNR: 2022-01516-01) and AMORIS (DNR: 2020–01545) were approved by the Swedish Ethical Review Authority. All procedures involving human subjects of the UK Biobank were approved by the NHS National Research Ethics Service (16/NW/0274). All participants of the UK Biobank and AMORIS cohort provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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