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Original Research

COPD and 20-year hearing decline: The HUNT cohort study

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A B S T R A C T

Background: We aimed to assess the association between chronic obstructive pulmonary disease (COPD) and long-term hearing decline. A further aim was to study sex differences.

Methods: Population-based cohort study in Norway (the HUNT study) with baseline measurements in 1996–1998 and follow-up in 2017–2019. The sample included 12,082 participants (43% men, mean age at follow-up 64 years). We used multiple linear regression to assess the association between COPD (minimum one registered ICD-10 code with emphysema or other COPDs during follow-up) and 20-year hearing decline in the low/mid/high frequency area (0.25–0.5/1–2/3-8 kHz). We adjusted for age, sex, education, smoking, noise exposure, ear infections, hypertension and diabetes.

Results: Persons registered with COPD (N = 403) had larger 20-year hearing decline at low frequencies (1.5 dB, 95% confidence interval (CI) 0.6–2.3) and mid frequencies (1.2 dB, 95% CI 0.4–2.1), but not at high frequencies. At high frequencies, the association was stronger and statistically significant only among women (1.9 dB, 95% CI 0.6–3.2). Persons registered with both COPD and respiratory failure (N = 19) had larger 20-year hearing decline at low and mid frequencies: 7.4 dB (95% CI 3.6–11.2) and 4.5 dB (95% CI 0.7–8.4), respectively.

Conclusion: Our large cohort study shows an association between COPD and increased long-term hearing decline. Women seem to be more susceptible to COPD-related hearing loss at high frequencies. The findings support that COPD can affect the cochlear function.

1. Introduction

Hearing loss is a common condition with complex pathophysiology. Relevant mechanisms for the genesis of sensorineural hearing loss include hypoxia, a state in which oxygen is not available in sufficient amounts at the tissue level to maintain adequate homeostasis. The cochlea requires high oxygen supply to maintain its function, and many animal studies have evaluated various mechanisms showing that hypoxia can affect the inner ear [1–4].

Chronic obstructive pulmonary disease (COPD) is a prevalent lung disease associated with chronic inflammation and reduced blood oxygen saturation. Studies have shown an association between COPD and poorer pure tone hearing threshold [5–10], suggesting that COPD can affect the cochlear function. However, most studies are cross-sectional, use small samples or have poor confounder control. As sex contributes to differences in disease risk, prevalence and presentation for both COPD [11] and hearing loss [12], one could also expect sex differences in COPD-related hearing loss.

To contribute towards better understanding of the pathophysiology of hearing loss, this large population-based follow-up study aims to assess the extent to which COPD is associated with long-term hearing threshold decline. A further aim is to study possible sex differences, which has not been evaluated previously.

2. Methods

2.1. Participants

The Trøndelag Health Study (HUNT) is one of the world's largest population-based health studies. HUNT started in 1984 and has been conducted in four waves (HUNT1-4). The HUNT study has been described in detail previously [13]. The second and fourth waves included hearing investigations with pure tone audiometry, namely HUNT2 hearing (1996–1998) and HUNT4 hearing (2017–2019). The HUNT2 hearing study included 50,560 participants (participation rate 61%), whereas the HUNT4 hearing study included 28,388 participants (participation rate 43%). The HUNT hearing studies have been

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described in detail previously [14]. The present longitudinal study included the 13,022 individuals who attended both hearing studies. The study was approved by The Regional Committee for Medical Research Ethics (23,178 HUNT Hearing).

2.2. Measurements

Exposure variable. We used data from the Norwegian Patient Registry [15] to assess COPD. The *Norwegian Patient Registry* contains information on everyone who is referred for or has received specialized healthcare at a hospital, outpatient clinic or from contract specialists. We defined COPD as receiving at least one ICD-10 code J43 (emphysema) or J44 (other COPD) between 2007 and 2019. We also used ICD-10 code J96 (respiratory failure with partial oxygen pressure <8 kPa). We did not have ICD-10 codes before 2007.

Outcome variable. Pure tone audiometry was conducted in line with ISO 8253-1 (International Organization for Standardization, 2010), with fixed frequencies at test frequencies 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz, utilizing an automatic procedure. Hearing thresholds were defined relative to the hearing threshold levels of the population of otologically normal subjects aged 19–23 years in each wave [14]. To evaluate the association between COPD and hearing decline at various frequencies, we used the pure tone average (PTA) in the low/mid/high frequency areas (0.25–0.5/1–2/3-8 kHz), mean of both ears. We defined hearing decline as the difference in hearing threshold between the baseline study (HUNT2, 1996–1998) and the follow up study (HUNT4, 2017–2019). As secondary outcomes we estimated binaural thresholds at each specific frequency.

Covariates. We used register data from Norwegian Statistics [16] to assess higher education measured at baseline (tertiary education, such as university). We used the baseline study questionnaire and measurements to assess diabetes mellitus (present or previous), hypertension (systolic blood pressure >140, average of 2. and 3. measurement), recurrent ear infections and occupational noise exposure (regularly exposed to loud noise at work, assessed as a categorical variable and scored as never exposed (reference category); <5 h weekly; 5–10 h weekly or >15 h weekly). We used both questionnaires to assess smoking (daily smoking at both studies; smoking but not daily at both studies; never smoked). The smoking variable was categorical with "never smoked" as the reference category. Missing values of all covariates (<5% for each covariate) were set to non-exposed.

2.3. Statistical analyses

We analysed data in Stata version 17.0. The statistical tests were calculated at 95% confidence interval (CI). We used multiple linear regression analyses to assess the association between COPD (yes/no) and 20-year hearing decline in the low/mid/high frequency ranges. We adjusted for age, sex, education, smoking, hypertension, diabetes and recurrent ear infections. Age was modelled as a restricted cubic spline with four knots to account for non-linearity, which created a better model fit than models with age as a linear variable (Likelihood-ratio test, P-value <0.001). We performed the analyses in the total sample, stratified by sex and by age group (>70 years at follow-up).

In order to estimate whether the association between COPD and 20-year hearing decline depended on sex, we performed interaction analyses (interaction term COPD*sex). We further performed subgroup analyses for COPD cases who were also registered with respiratory failure, or who had at least two registrations with COPD.

Finally, we performed frequency-specific secondary analyses with separate regression models for each of the eight frequencies. We present adjusted mean 20-year hearing decline for persons with or without COPD with covariates set at their mean.

3. Results

3.1. Participants

Among the 13,022 participants who took part in both hearing studies, we excluded persons with missing questionnaires (N = 886) or incomplete audiometry (N = 54). Table 1 displays the characteristics of the final sample (N = 12,082). The sample included 43% men, and mean age at follow-up was 64 years (age range 40–99 years). Compared with persons not registered with COPD during follow-up (reference group, N = 11,679), the COPD group (N = 403) were older (mean age 71 years versus 64 years), had higher prevalence of daily smokers (16% versus 7%) and lower prevalence of high education (14% versus 26%).

Among the 403 COPD cases, 388 cases were registered with ICD-10 code J44 (mean number of registrations 4.6, SD 6.2, range 1–50), whereas 47 cases were registered with ICD-10 code J43 (mean number of registrations 1.7, SD 1.3, range 1–8). Altogether 19 cases were registered with both COPD (J44 or J43) and respiratory failure (J96).

Covariates: Diabetes, blood pressure, education and occupational noise exposure (>15 h weekly) were measured at the baseline study (1996–1998). Smoking was measured at both baseline and follow-up.

3.2. Regression analyses

Table 2 shows the results from the regression analyses. COPD was associated with increased 20-year hearing decline at low frequencies (1.5 dB, 95% confidence interval (CI) 0.6–2.3) and at mid frequencies (1.2 dB, 95% CI 0.4–2.1), but not at high frequencies (0.7 dB, 95% CI -0.3-1.7).

Interaction analyses showed stronger association between COPD and 20-year hearing decline among women than men at high frequencies (p < 0.001), but not at low or mid frequencies. Stratified analyses showed that among women, COPD was associated with 1.9 dB (95% CI 0.6–3.2) larger 20-year hearing decline at high frequencies. For men, no statistically significant association at high frequencies was shown (−0.5, 95%

Table 1
Characteristics of the 12,082 participants. The HUNT study, Norway. Baseline study 1996–1998, follow-up study 2017–2019.

	Total sample (N = 12,082)	COPD (N = 403)	No COPD (N = 11,679)
Age at follow-up, mean (range)	64 (40–99)	71 (42–92)	64 (40–99)
Men, N (%)	5235 (43)	185 (46)	5050 (43)
Hearing threshold at baseline			
PTA 250–500 kHz, dB, mean (SD)	5.3 (7.4)	7.2 (8.1)	5.3 (7.4)
PTA 1–2 kHz, dB, mean (SD)	6.3 (8.4)	9.3 (9.4)	6.2 (8.4)
PTA 3–8 kHz, dB, mean (SD)	15.1 (14.7)	21.8 (16.6)	14.9 (14.6)
Hearing decline during follow-up			
PTA 250–500 kHz, dB, mean (SD)	3.1 (9.0)	6.3 (9.9)	2.9 (8.9)
PTA 1–2 kHz, dB, mean (SD)	9.3 (9.8)	13.5 (11.2)	9.1 (9.7)
PTA 3–8 kHz, dB, mean (SD)	17.1 (11.6)	21.3 (11.3)	16.9 (11.6)
Higher education, N (%)	3048 (25)	57 [14]	2991 (26)
Occupational noise exposure, N (%)	1381 [11]	79 [20]	1302 [11]
Daily/some smoking, N (%)	899 [8]/6423 (53)	63 [16]/292 (72)	836 [7]/6131 (53)
Systolic blood pressure >140, N (%)	2632 [22]	94 (23)	2538 [22]
Diabetes mellitus, N (%)	114 [1]	7 [2]	107 [1]
Recurrent ear infections	2478 [21]	90 [22]	2388 [20]

COPD (chronic obstructive pulmonary disease), PTA (pure tone average).

Table 2
Associations between COPD and 20-year hearing decline among 12,082 participants. The HUNT study, Norway. Baseline study 1996–1998, follow-up study 2017–2019.

	PTA 0.25–0.5 kHz Coefficient, dB (95% CI)	PTA 1–2 kHz Coefficient, dB (95% CI)	PTA 3–8 kHz Coefficient, dB (95% CI)
Total sample	**1.5 (0.6–2.3)***	**1.2 (0.4–2.1)***	0.7 (−0.3–1.7)
Women	**1.5 (0.3–2.7)***	**1.5 (0.4–2.7)***	**1.9 (0.6–3.2)***
Men	**1.4 (0.2–2.7)***	0.9 (−0.4–2.1)	−0.5 (−2.1–1.0)
Age =<70 years	0.6 (−0.6–1.7)	0.6 (−0.5–1.7)	1.1 (−0.3–2.5)
Age >70 years	**2.3 (0.9–3.6)***	**1.9 (0.5–3.3)***	0.6 (−0.8–2.1)

COPD: chronic obstructive pulmonary disease, PTA: Pure tone average.
Multiple linear regression adjusted for age, sex, education, smoking, hypertension, diabetes and recurrent ear infection.
*P < 0,05.

CI -2.1-1.0).

Subgroup analyses (not tabulated). Cases who were registered with both COPD and respiratory failure (N = 19) had larger 20-year hearing decline than the reference group at low and mid frequencies: 7.4 dB (95% CI 3.6–11.2) and 4.5 dB (95% CI 0.7–8.4), respectively. COPD cases with minimum two registrations of J43 or J44 (N = 247) had larger 20-year hearing decline at low and mid frequencies: 1.4 dB (95% CI 0.3–2.4) and 1.2 dB (95% CI 0.1–2.2) respectively.

Frequency-specific secondary analyses (Figs. 1 and 2). We finally performed frequency-specific analyses with separate regression models for the eight frequencies. Fig. 1 illustrates the adjusted differences in 20-year hearing decline between persons with or without COPD at each frequency. There were stronger associations at low and mid frequencies. Fig. 2 illustrates adjusted mean 20-year hearing decline for persons with or without COPD at each specific frequency. As expected, the 20-year hearing decline was larger at high frequencies for all participants.

4. Discussion

4.1. Main findings

Our large cohort study showed an association between COPD and increased long-term hearing decline at low and mid frequencies. Among

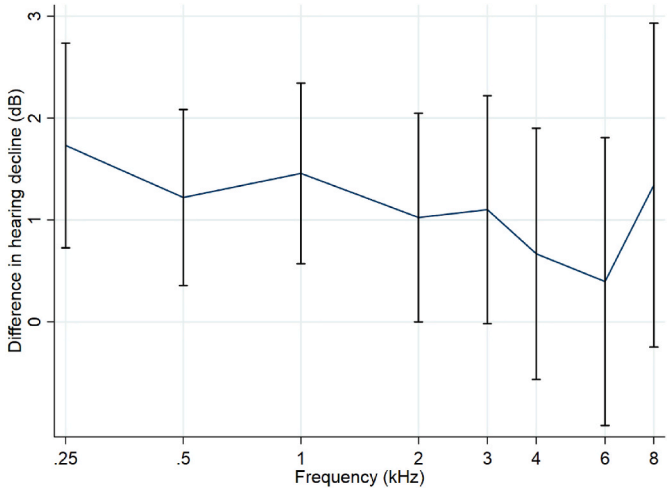
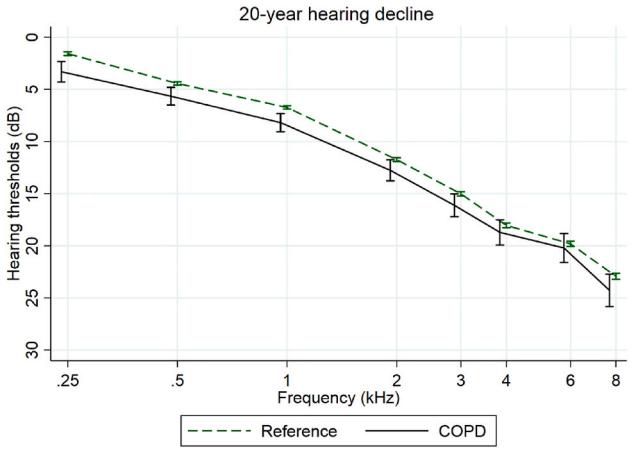
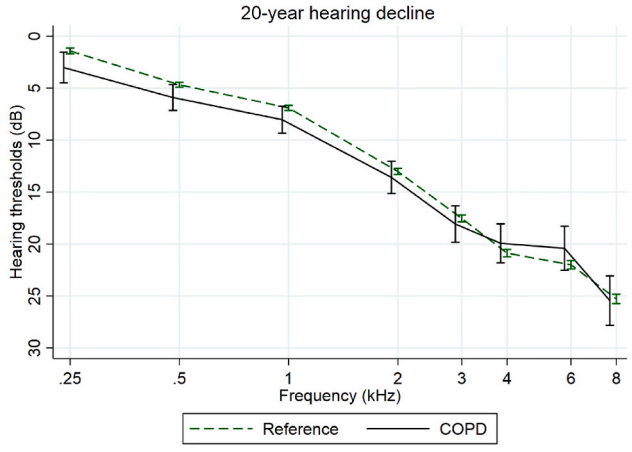


Fig. 1. Mean difference in 20-year hearing decline between persons with or without COPD. Linear regression adjusted for age, sex, education, smoking, hypertension, diabetes and recurrent ear infections. The HUNT study, Norway. Baseline study 1996–1998, follow-up study 2017–2019.

A. Total sample



B. Men



C. Women

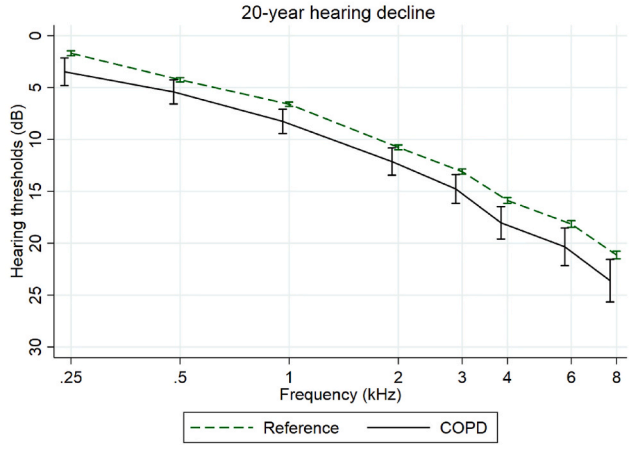


Fig. 2. Mean 20-year hearing threshold decline for persons with or without COPD with covariates set at their mean. Linear regression adjusted for age, sex, education, smoking, hypertension, diabetes and ear infections. The HUNT study, Norway. Baseline study 1996–1998, follow-up study 2017–2019.

persons registered with both COPD and respiratory failure, the associations were even stronger. At high frequencies, the association between COPD and 20-year hearing decline was statistically significant only among women.

4.2. COPD and pure tone hearing threshold: comparison with other studies

Our study showed an association between COPD and poorer pure tone hearing thresholds, which complies with prior findings. A recent meta-analysis [5] that evaluated four studies of COPD and audiometry threshold included altogether 115 subjects with COPD and 40 controls [6–9]. The meta-analysis showed that the overall pooled mean hearing thresholds were higher in patients with COPD than controls, with a standardized mean difference of 1.8 dB, 95% CI 0.4–3.1. The effect size agrees with our results. The meta-analysis further reported higher standardized mean differences between COPD and controls for low frequencies (0.5 and 1 kHz) than higher frequencies, which also complies with our finding. A later population-based study of COPD and pure tone audiometry threshold provided a larger sample size with 203 persons with COPD, which was assessed as an FEV1/FVC of less than 70% [10]. The study showed that COPD was associated with worse hearing at each frequency, yet stronger at high frequencies (3.3 dB, 95% CI: 1.5, 5.1) than low frequencies (2.3 dB, 1.1, 3.5). We believe our large cohort study adds important support to these prior cross-sectional results and strengthens the theory on COPD and poorer hearing threshold.

4.3. Possible biological explanations

The cochlea requires oxygen to maintain its function and is highly sensitive to reduced blood supply. Many experimental animal studies have evaluated various mechanisms showing that hypoxia can affect the cochlear function [1–4]. For example, it has been showed that the cochlea is vulnerable to blockade of cochlear blood flow and interruption of the oxygen supply [1]. COPD is often associated with a chronic decrease in the partial pressure of oxygen (pO2). As such, this could explain the relationship between COPD and poorer hearing thresholds. Regarding the stronger association at the lower frequencies, it has been suggested that the cochlear apex, which is responsible for lower frequency hearing, has fewer capillary vessels making it more vulnerable to hypoxemia [5].

In addition to the theory on hypoxemia, it has been speculated whether the observed auditory affection in persons with COPD can reflect shared inflammatory mechanisms by COPD and hearing loss [15]. COPD is associated with a low-grade systemic inflammation, which potentially relates COPD to other systemic manifestations of the disease, such as cardiovascular disease [17]. In a similar way, the inflammatory cells or mediators in COPD could be relevant to the worsening of hearing thresholds.

As to other possible affections of the auditory system, it has been reported that COPD is related with retrocochlear pathology. Studies have shown an association between COPD and prolonged auditory brainstem responses [18,19], indicating that COPD may also be related with certain dysfunctions of the central auditory pathways.

4.4. Sex differences

Sex contributes to differences in disease risk, prevalence and presentation for both COPD [11,20] and hearing loss [12]. As such, we aimed to investigate possible sex differences in COPD-related hearing loss. The present interaction analyses showed stronger associations between COPD and hearing decline among women than men at high frequencies. To our knowledge, no study has evaluated possible sex differences in the relation between COPD and hearing. We can only speculate about possible underlying mechanisms. It is well-known that women with COPD may present differently and may have a different pattern of comorbidities compared with men [11,20]. For example, women with COPD are more likely to have a chronic bronchitis phenotype, suffer from less cardiovascular comorbidity, have more concomitant depression and osteoporosis [20]. Although not directly comparable, a prior study showed that the association between smoking and high-frequency hearing loss, assessed as a decrease in acoustic absorbance rates, occurred with less smoking exposure in women than men [21].

4.5. Strengths and limitations

Strengths include the standardized audiometric measurements, good confounder control with prospective measurements, a large data set with many COPD cases and a population-based follow-up design, in which the population has been assessed to be representative for the entire country [22].

A limitation of our study is lack of spirometry and data on COPD duration. COPD was defined as minimum one registered ICD-10 code J43 (emphysema) or J44 (other COPDs) during follow-up. The COPD diagnosis was however set by a specialist, and as a rule based on in-depth investigations including spirometry. As to COPD severity, analyses including COPD cases with respiratory failure showed even stronger associations. We had no COPD data before 2007, but we believe many persons with short-time mild COPD have most likely only been examined in primary care. We believe our study entails a reliable COPD diagnosis and sufficient exposure during follow-up. We had no data on the time of onset of COPD. We expect that the younger participants with COPD had shorter duration of the disease and milder hypoexmia than the older participants. This could explain the somewhat stronger association between COPD and hearing decline among older persons compared with younger persons. On the other hand, the older participants with COPD were maybe exposed already before study start. This may have underestimated their results, since their hearing was perhaps already affected before the study started. Finally, we cannot eliminate weaker associations due to loss to follow-up among participants with poorer health (COPD) and hearing loss.

5. Conclusion

Our large cohort study showed an association between COPD and increased long-term hearing decline., Our study also suggests that women may be more vulnerable to COPD-related high frequency hearing loss. The effect sizes were small, and we believe the clinical implications with respect to persons with COPD are limited. Our study adds strengths to prior findings and contributes towards better understanding of the pathophysiology of hearing loss.

Author contribution

The manuscript has been read and approved by all authors. All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Declaration of competing interest

None.

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and the Norwegian Institute of Public Health.

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