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RESEARCH ARTICLE

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# Urban–rural differences in pneumonia risk in patients with chronic obstructive pulmonary disease: a nationwide register-based study

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**ABSTRACT**

**Background:** Urban–rural differences in treatment within chronic obstructive pulmonary disease (COPD) have been documented in Denmark, and we aim to investigate such differences in the risk of pneumonia.

**Methods:** A Danish register-based cross-sectional study including patients with an International Classification of Diseases 10th revision (ICD-10) diagnosis code of COPD (J.44) alive on the 31st of December 2018 (99,057 patients). Patients were grouped by municipality type on an urban–rural gradient (capital, metropolitan, provincial, commuter, rural). We identified outpatient pneumonias (redeemed prescriptions of antibiotics typically used for pneumonia) and pneumonia hospitalizations (ICD-10 codes) during 2018. Three groups were defined: 1) No pneumonia, 2) at least one outpatient pneumonia (but no pneumonia hospitalization), and 3) at least one pneumonia hospitalization. A multivariable multinomial logistic regression model was performed with municipality type as main explanatory variable. The 'No pneumonia' group was used as reference outcome group.

**Results:** Patients outside capital municipalities had significantly increased risk of experiencing outpatient pneumonia (Metropolitan: Odds ratio (OR) = 1.32, 95% confidence interval (CI): 1.25–1.39. Provincial: OR = 1.26, 95% CI: 1.21–1.31. Commuter: OR = 1.25, 95% CI: 1.20–1.31. Rural: OR = 1.28, 95% CI: 1.23–1.33). No significant differences were found for pneumonia hospitalization.

**Conclusions:** Compared to patients in capital municipalities, patients with a hospital-registered COPD diagnosis in non-capital municipalities had a higher risk of annually redeeming at least one prescription for antibiotics typically used for outpatient pneumonia. We were unable to detect differences in pneumonia hospitalization between municipality types. Our study was not designed to assess causality, and we stress the need for future research to provide actionable insights for health policy makers.

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Urban–rural; chronic obstructive pulmonary disease; pneumonia; socio-economic status; register-based; epidemiology

## Introduction

Chronic obstructive pulmonary disease (COPD) is an airway disease that is characterized by airway inflammation and respiratory symptoms such as dyspnea, cough, and increased sputum production. Patients with COPD have both an increased risk of pneumonia as well as more severe pneumonias compared to the background population [1,2], and pneumonia in patients with COPD is linked to increased mortality [3–5]. Pneumonia, in general, is the leading infectious cause of death in both Europe and the United States [6,7].

Both COPD and pneumonia risk have been associated with low socio-economic status (SES) [8,9], and low SES is increasingly linked to urban–rural differences [10–12]. Such differences have mostly been studied within COPD in the United States (USA), where rural residence is associated with higher COPD prevalence, mortality, and morbidity [13–15]. These results may not be generalized to a European context where wealth and income inequalities and spatial wage disparities are generally lower [16–19]. Despite this, geographical inequalities in health are well-recognized in Denmark, and they have been stated by the Danish Ministry of Health as a major health problem [20].

To the best of our knowledge, no studies have investigated urban–rural differences in pneumonia risk within COPD in a Danish or European context.

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Our study aims to investigate this, with the hypothesis that patients living in non-capital municipalities have an increased risk of pneumonia.

## Methods

### Data sources and study design

This was a nationwide Danish register-based cross-sectional study with data from 2018. The study utilized the study population of a previous serial cross-sectional study with data up until the year 2018 [21], and we included all patients with an ICD-10 code of COPD (J.44) who were alive on the 31st of December of 2018. Demographic and socio-economic data were collected from Statistics Denmark (DST), International Classification of Diseases 10th Revision (ICD-10) diagnosis codes were collected from the Danish National Patient Register (DNPR), and Anatomical Therapeutical Chemical (ATC) codes from redeemed prescriptions were collected from the Danish National Prescription Register (NPR). Data were linked via a unique personal identification number, which is given to every inhabitant in Denmark.

### Study variables

#### Pneumonia

We identified both outpatient pneumonias and pneumonia hospitalizations during 2018 and divided patients into three categories: 1) Patients without pneumonia during the year, 2) patients with at least one annual outpatient pneumonia, and 3) patients with at least one annual pneumonia hospitalization. An outpatient pneumonia was defined as a redeemed prescription of antibiotics typically used for pneumonia. A pneumonia hospitalization was defined by ICD-10 codes of pneumonia from both hospitalizations and ER-visits. ATC codes and ICD-10 codes are displayed in Table 1.

#### Urban–rural differences

The explanatory variable of primary interest of our study was place of residence on municipality level on an urban–rural gradient, and DST has designed a municipality type variable specifically to investigate this (capital municipality, metropolitan municipality, provincial municipality, commuter municipality, and rural municipality) [22]. This variable includes two important aspects of geographical differences: population density and geographical remoteness [22,23]. The Danish municipalities by municipality type are shown in Figure 1.

#### Confounding variables

We collected the demographic and socio-economic variables sex, age, co-habitation status (living alone or co-habiting), and educational level (primary, secondary, vocational, college). Educational level refers to the highest completed education of the patient. Short college, medium college, and Master/PhD were summed into 'College'. We calculated the Charlson Comorbidity Index (CCI) according to Quan et al. from ICD-10 codes 3 years prior to index date [24]. Inhaled corticosteroid (ICS) doses were calculated from the accumulated dose of redeemed prescriptions during the year and grouped according to ICS dose (No ICS, low dose, medium dose, high dose) based on standard-particle beclomethasone dipropionate equivalents like in previous studies [25,26].

### Statistical analysis

We calculated the distribution of patients for each categorical variable including age in 10-year intervals, for both the total population and by municipality type. We also calculated mean and standard deviation for age as a continuous variable. The proportion of patients who experienced at least one outpatient pneumonia or pneumonia hospitalization was determined for each municipality and for each municipality type.

**Table 1.** Codes used for identifying pneumonia.

| Moderate pneumonia (ATC codes) | Severe pneumonia (ICD-10 codes) |
|---|---|
| • J01CA04: amoxicillin | • J12: viral pneumonias |
| • J01CA02: ampicillin | • J13–18: bacterial pneumonias and pneumonia from unspecified organisms |
| • J01CE02: phenoxymethylpenicillin | • A481: legionnaires' disease |
| • J01CR01: ampicillin and beta-lactamase inhibitor | • A709: ornithosis |
| • J01CR02: amoxicillin and beta-lactamase inhibitor | • B012: varicella pneumonia |
| • J01FA01: erythromycin | |
| • J01FA06: roxithromycin | |
| • J01FA09: clarithromycin | |
| • J01FA10: azithromycin | |

Abbreviations: ATC = anatomical therapeutic chemical. ICD-10 = International Classification of Diseases 10th Revision.

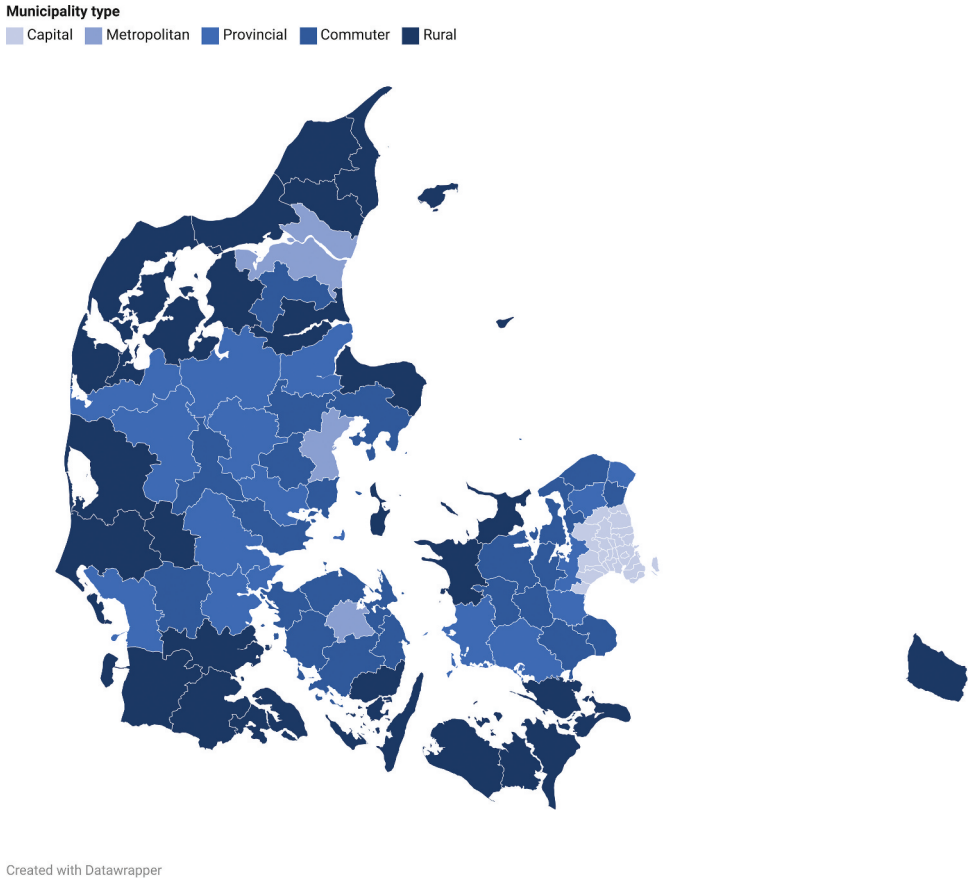


**Figure 1.** Danish municipalities by municipality type.*
*First published by Klitgaard et al. [22].

We excluded four small island municipalities from analysis due to few observations.

We estimated risk of pneumonia between municipality types for both outpatient pneumonia and pneumonia hospitalization with a multinomial logistic regression model with the following groups as outcome variable: 1) No pneumonia during the year, 2) at least one outpatient pneumonia (but no pneumonia hospitalization) during the year, and 3) at least one pneumonia hospitalization during the year. The 'No pneumonia' group was used as reference, and the model was adjusted for age, sex, educational level, cohabitation status, and CCI. We used a significance level of 5%. SAS 9.4 TS Level 1M5 (SAS, Inc., Cary, NC, USA) was used for all analyses.

## Results

Table 2 shows study population characteristics. A slightly larger proportion of patients in capital municipalities were female (56.6%) compared to rural municipalities (52.3%), and more patients in capital municipalities were living alone (58.5% vs 49.1%). The educational level of patients in capital municipalities was higher than in rural municipalities. There were no observable differences between municipality types in sex or comorbidities (CCI).

Figure 2 is a map of Danish municipalities showing the proportion of patients in each municipality that experienced at least one outpatient pneumonia or pneumonia hospitalization. While a pattern emerges of more patients experiencing outpatient pneumonias outside capital municipalities, no such pattern is seen regarding hospitalizations. The underlying data for Figure 2 are in Appendix A, Table S1. Table 3 and Figure 3 show the distribution by municipality type of patients that experienced at least one outpatient pneumonia or pneumonia hospitalization. In capital municipalities compared to other municipalities, a smaller proportion of patients experienced outpatient pneumonia, while a larger proportion of patients did not experience pneumonia at all.

Table 4 shows the results from the multinomial logistic regression model. The risk of having at least one outpatient pneumonia was significantly higher in all municipality types compared to capital

**Table 2.** Study population characteristics in total and by municipality type.

| | Total population | | Capital municipalities | | Metropolitan municipalities | | Provincial municipalities | | Commuter municipalities | | Rural municipalities | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 25,665 | | 9,708 | | 22,536 | | 16,746 | | 24,402 | |
| N | n | % | n | % | n | % | n | % | n | % | n | % |
| Sex | | | | | | | | | | | | |
| Male | 45,396 | 45.8 | 11,141 | 43.4 | 4,312 | 44.4 | 10,347 | 45.9 | 7,956 | 47.5 | 11,640 | 47.7 |
| Female | 53,661 | 54.2 | 14,524 | 56.6 | 5,396 | 55.6 | 12,189 | 54.1 | 8,790 | 52.5 | 12,762 | 52.3 |
| **Mean age (SD)** | 71.8 | (10.4) | 71.5 | (10.6) | 72.6 | (10.3) | 71.9 | (10.4) | 72.0 | (10.3) | 71.8 | (10.3) |
| **Age group** | | | | | | | | | | | | |
| 40–49 | 1,674 | 1.7 | 467 | 1.8 | 126 | 1.3 | 421 | 1.9 | 254 | 1.5 | 406 | 1.7 |
| 50–59 | 11,239 | 11.3 | 3,191 | 12.4 | 989 | 10.2 | 2,482 | 11.0 | 1,893 | 11.3 | 2,684 | 11.0 |
| 60–69 | 26,170 | 26.4 | 6,895 | 26.9 | 2,497 | 25.7 | 5,846 | 25.9 | 4,282 | 25.6 | 6,650 | 27.3 |
| 70–79 | 35,745 | 36.1 | 9,118 | 35.5 | 3,471 | 35.8 | 8,287 | 36.8 | 6,200 | 37.0 | 8,669 | 35.5 |
| 80+ | 24,229 | 24.5 | 5,994 | 23.4 | 2,625 | 27.0 | 5,500 | 24.4 | 4,117 | 24.6 | 5,993 | 24.6 |
| **Charlson Comorbidity Index** | | | | | | | | | | | | |
| 0 | 82,400 | 83.2 | 21,408 | 83.4 | 8,068 | 83.1 | 18,590 | 82.5 | 13,874 | 82.8 | 20,460 | 83.8 |
| 1 | 6,427 | 6.5 | 1,809 | 7.0 | 585 | 6.0 | 1,466 | 6.5 | 1,107 | 6.6 | 1,460 | 6.0 |
| 2 | 7,779 | 7.9 | 1,821 | 7.1 | 809 | 8.3 | 1,882 | 8.4 | 1,361 | 8.1 | 1,906 | 7.8 |
| 3+ | 2,451 | 2.5 | 627 | 2.4 | 246 | 2.5 | 598 | 2.7 | 404 | 2.4 | 576 | 2.4 |
| **Inhaled corticosteroid dose** | | | | | | | | | | | | |
| No ICS | 57,072 | 57.6 | 15,999 | 62.3 | 5,435 | 56.0 | 12,591 | 55.9 | 9,453 | 56.4 | 13,594 | 55.7 |
| Low dose | 14,782 | 14.9 | 4,011 | 15.6 | 1,436 | 14.8 | 3,295 | 14.6 | 2,424 | 14.5 | 3,616 | 14.8 |
| Medium dose | 17,931 | 18.1 | 4,016 | 15.6 | 1,861 | 19.2 | 4,291 | 19.0 | 3,136 | 18.7 | 4,627 | 19.0 |
| High dose | 9,272 | 9.4 | 1,639 | 6.4 | 976 | 10.1 | 2,359 | 10.5 | 1,733 | 10.3 | 2,565 | 10.5 |
| **Co-habitation status** | | | | | | | | | | | | |
| Living alone | 52,032 | 52.5 | 15,008 | 58.5 | 5,489 | 56.5 | 11,595 | 51.5 | 7,949 | 47.5 | 11,991 | 49.1 |
| Co-habiting | 47,025 | 47.5 | 10,657 | 41.5 | 4,219 | 43.5 | 10,941 | 48.5 | 8,797 | 52.5 | 12,411 | 50.9 |
| **Education** | | | | | | | | | | | | |
| Primary | 45,484 | 45.9 | 9,957 | 38.8 | 4,366 | 45.0 | 10,773 | 47.8 | 7,823 | 46.7 | 12,565 | 51.5 |
| Secondary | 1,687 | 1.7 | 704 | 2.7 | 192 | 2.0 | 276 | 1.2 | 247 | 1.5 | 268 | 1.1 |
| Vocational | 35,681 | 36.0 | 9,685 | 37.7 | 3,413 | 35.2 | 8,201 | 36.4 | 6,057 | 36.2 | 8,325 | 34.1 |
| College | 13,429 | 13.6 | 4,482 | 17.5 | 1,435 | 14.8 | 2,709 | 12.0 | 2,192 | 13.1 | 2,611 | 10.7 |
| Missing | 57,072 | 57.6 | 837 | 3.3 | 302 | 3.1 | 577 | 2.6 | 427 | 2.5 | 633 | 2.6 |

municipalities with odds ratios (ORs) ranging from 1.25 (95% Confidence interval (CI): 1.20–1.31) to 1.32 (95% CI: 1.25–1.36). No significant differences between municipality types were seen in the risk of having at least one pneumonia hospitalization.

## Discussion

In summary, we have documented nationwide urban–rural differences in 2018 in the risk of pneumonia in patients with a hospital-registered COPD diagnosis in Denmark, where patients in non-capital municipalities had a higher risk of having at least on annual outpatient pneumonia, but no such differences were seen regarding pneumonia hospitalization.

Multiple explanations may exist for the identified urban–rural differences in outpatient pneumonia risk. The simplest one is that patients outside capital municipalities have more severe disease, which has been documented in the USA within COPD and in general [12–15,27]. In our study, however, the burden of comorbidity measured by CCI was distributed equally between municipality types. In this regard, it is important to note the limitations of the CCI as a measure of disease burden. First, the CCI in our study measures only the diseases that have been registered in a hospital setting and thus does not capture the entirety of relevant comorbidities. Second, the CCI captures only the number of diseases, and not the severity of the individual diseases.

We were not able to detect urban–rural differences in the risk of pneumonia hospitalization, and this may have several explanations. The distance to a hospital could be a contributing factor [28]. A longer distance to hospital has been associated with less referrals and admissions in both the USA and Sweden – a country very similar to Denmark [29,30]. Another reason could be the inverse care law, where patients in capital municipalities having generally higher SES and, therefore, more likely to be referred to hospital [31]. With these two explanations combined, it may be speculated that patients outside capital municipalities in Denmark are more likely to be treated with antibiotics for a respiratory tract infection that may have resulted in a hospital admission for patients in capital municipalities. This would further explain our observed differences in outpatient pneumonias. The lack of association may also be explained by our study design as explained below. Finally, the well-established socio-economic differences in health in Denmark may not translate into urban–rural differences [32]. On the other hand, a lower use of ICS treatment has been documented in capital

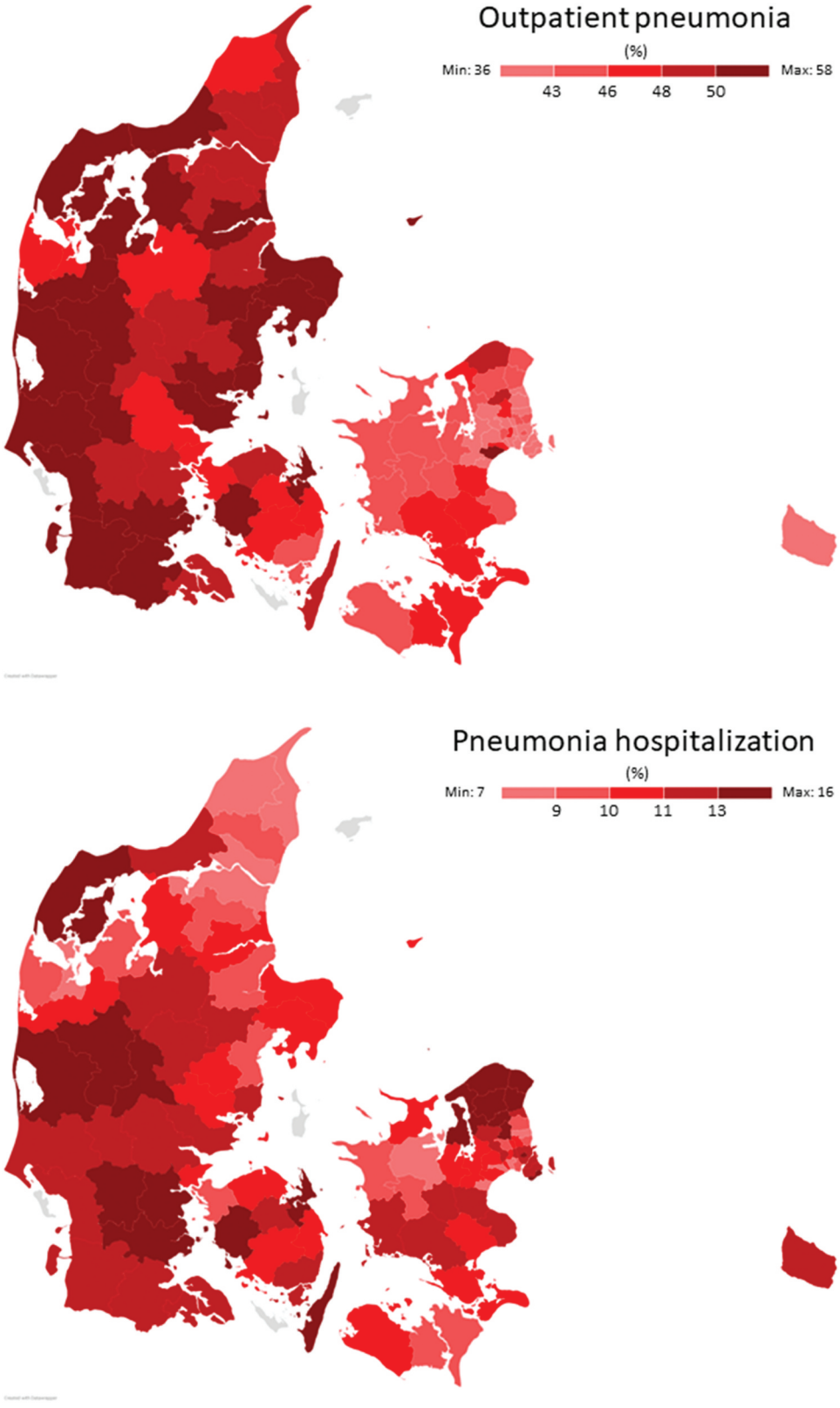


**Figure 2.** Proportion of patients in each municipality* who experienced at least one annual outpatient pneumonia or pneumonia hospitalization.

*The four municipalities with no data have been colored in grey.

**Table 3.** Proportion of patients by municipality type experiencing at least one outpatient pneumonia, one pneumonia hospitalization, or no pneumonia.*

| | Capital | | Metropolitan | | Provincial | | Commuter | | Rural | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 25,665 | | 9,708 | | 22,536 | | 16,746 | | 24,402 | |
| N | n | % | n | % | n | % | n | % | n | % |
| Outpatient pneumonia | 10,711 | 41.7 | 4,706 | 48.5 | 10,752 | 47.7 | 7,995 | 47.7 | 11,643 | 47.7 |
| Pneumonia hospitalization | 2,419 | 9.4 | 843 | 8.7 | 2,063 | 9.2 | 1,532 | 9.1 | 2,089 | 8.6 |
| No pneumonia | 14,362 | 56.0 | 4,869 | 50.2 | 11,416 | 50.7 | 8,511 | 50.8 | 12,390 | 50.8 |

*Proportions do not add up to 100%, as one patient can experience both outpatient pneumonias and pneumonia hospitalizations.

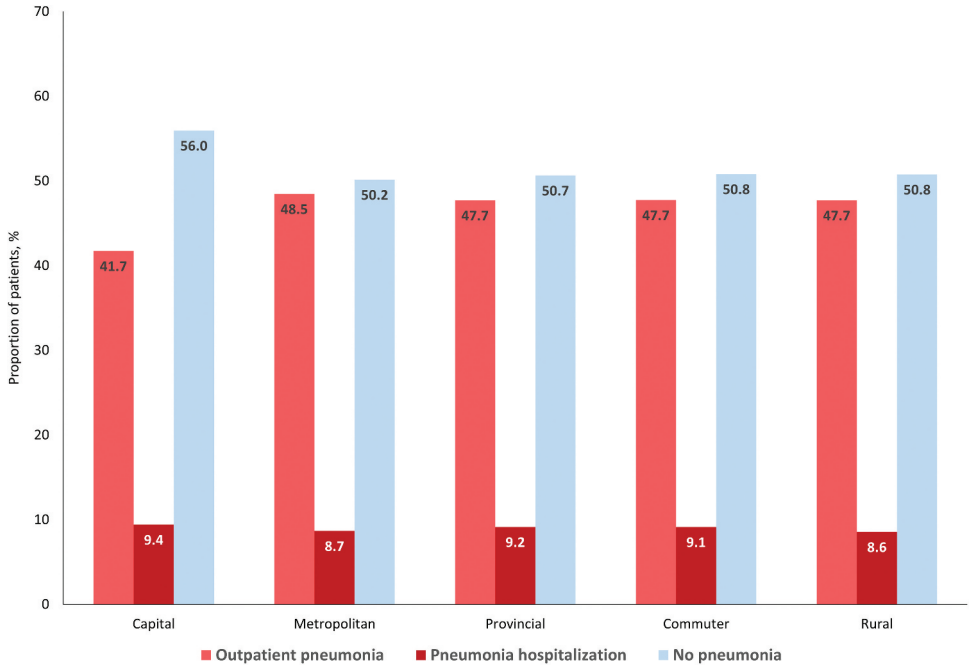


**Figure 3.** Proportion of patients by municipality type experiencing at least one outpatient pneumonia, one pneumonia hospitalization, or no pneumonia.*
*Proportions do not add up to 100%, as one patient can experience both outpatient pneumonias and pneumonia hospitalizations.

**Table 4.** Multinomial logistic regression model for the three pneumonia groups, with 'no pneumonia' as reference group (adjusted for sex, age, educational status, partner status, and Charlson comorbidity index).

| | OR | (95% CI) | p-value |
|---|---|---|---|
| **At least one outpatient pneumonia*** | | | |
| Capital | Reference | | - |
| Metropolitan | 1.32 | 1.25–1.39 | <0.01 |
| Provincial | 1.26 | 1.21–1.31 | <0.01 |
| Commuter | 1.25 | 1.20–1.31 | <0.01 |
| Rural | 1.28 | 1.23–1.33 | <0.01 |
| **At least one pneumonia hospitalization** | | | |
| Capital | Reference | | - |
| Metropolitan | 0.98 | 0.90–1.07 | 0.59 |
| Provincial | 1.03 | 0.96–1.10 | 0.43 |
| Commuter | 1.04 | 0.96–1.11 | 0.33 |
| Rural | 0.98 | 0.91–1.04 | 0.47 |

*But no pneumonia hospitalization. Abbreviations: OR = adjusted odds ratio. CI = confidence interval.

municipalities in Denmark [26], and ICS treatment may be considered a proxy of disease severity [33–37]. Both disease severity and ICS treatment are independently associated with risk of pneumonia hospitalization [38,39], and it appears likely that patients in capital municipalities would have a lower risk of pneumonia hospitalization compared to patients living outside capital municipalities.

### *Strengths and limitations*

Some limitations must be discussed. First, ICD-10 codes are only registered upon hospital contact in Denmark, which may cause selection bias. Patients with COPD without hospital contacts were not included in our study, and these patients are likely to have less severe disease [40,41]. Second, our results may not be generalizable to other countries where healthcare and societal structures are different. However, it occurs likely that these differences may be documented in larger countries with more pronounced socio-economic inequality than in Denmark. Third, our definition of outpatient pneumonia may misclassify both other infections and exacerbations as pneumonias. Pneumonia is often clinically defined by an infiltration on a chest radiograph, but these are often not obtained in an outpatient setting, where clinical presentation is used to diagnose pneumonia. We believe our approach to be viable for several reasons: the clinical distinction of exacerbation vs pneumonia is difficult and they may not even be seen as two distinct etiological entities [42], and chest radiography may have limited predictive value in this distinction [43,44]. Furthermore, the use of antibiotics in Denmark is low [45], and it has even decreased from 2012 to 2021 [46], which minimizes this risk of misclassification. Nevertheless, it is possible that our results reflect a higher risk of infections in general. Fourth, the study design is not well-suited to assess causal relationships. We consider our study to be cross-sectional in design with patients grouped according to the previous year's pneumonia occurrence – similar to how patients with COPD are routinely stratified into GOLD groups by the assessment of exacerbations during the preceding year [47] – and a cohort study design would be better suited to assess causal relationships between rural–urban living and pneumonia risk. However, these were the data available to us, and our study is currently the best available evidence towards such disparities. Lastly, our study lacks data on potentially confounding clinical factors such as smoking status and pulmonary function, and some residual bias may be expected [21].

Our study has several considerable strengths. The validity of our register data is high [28,48–53], and data are virtually complete with only a minor proportion of data missing on educational status. Despite the limitations, our study provides the best currently available evidence regarding urban–rural differences in COPD in Denmark.

## Conclusions

Our study documents possible urban–rural differences in the risk of pneumonia in patients with a hospital-registered COPD diagnosis in Denmark. Patients in non-capital municipalities experienced higher risk of annually redeeming at least one prescription for antibiotics typically used for outpatient pneumonia, but we were unable to detect such differences regarding pneumonia hospitalization. Our study does not allow for the assessment of a causal relationship, and we urge researchers to investigate urban–rural disparities in COPD in studies specifically designed to uncover actionable insights, as such evidence may guide policy makers in improving patient care.

## Disclosure statement

Rikke Ibsen is a co-owner of the private statistics consulting company i2minds. Rikke Ibsen has no financial gains from the publication of this manuscript.

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## Abbreviations

| | |
|---|---|
| COPD | chronic obstructive pulmonary disease |
| CCI | Charlson Comorbidity Index |
| CI | confidence interval |
| DNPR | Danish National Patient Register |
| DST | Statistics Denmark |
| ICD-10 | International Classification of Diseases 10th Revision |
| ICS | inhaled corticosteroid |
| NPR | Danish National Prescription Register |
| OR | odds ratio |
| SES | socio-economic status |
| USA | United States of America |

## Author contribution

**Allan Klitgaard**: conceptualization, methodology, resources, writing – original draft, writing – review and editing, visualization, project administration, funding acquisition. **Rikke Ibsen**: methodology, formal analysis, investigation, resources, data curation, writing – review and editing, visualization. **Ole Hilberg**: Writing – review and editing, supervision, funding

acquisition. **Anders Løkke**: conceptualization, methodology, writing – original draft, writing – review and editing, supervision, project administration, funding acquisition.

## Data availability statement

Data from registers are not publicly available. The data supporting the conclusions of this article are available from registers upon request and approval of access by national authorities.

## Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. All data accessed complied with relevant data protection legislation. Research ethics approval is not required for register-based research according to Danish Law and National Ethics Committee Guidelines.

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