# Prescribing antibiotics: Factors associated with C-reactive protein testing in general practice. A register-based study

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**Research Article**

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# Prescribing antibiotics: Factors associated with C-reactive protein testing in general practice. A register-based study

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# Abstract

## Background

The use of C-reactive protein (CRP) tests is shown to safely reduce antibiotic prescribing for acute respiratory tract infections (RTIs). The aim of this study was to explore patient and clinical factors associated with the use of CRP testing when prescribing antibiotics recommended for RTIs.

## Methods

A nation-wide retrospective cross-sectional register-based study based on first redeemed antibiotic prescriptions issued to adults in Danish general practice between July 2015 and June 2017. Only antibiotics recommended for treatment of RTIs were included in the analysis (penicillin-V, amoxicillin, co-amoxicillin or roxithromycin/clarithromycin). Logistic regression models were used to estimate odds ratios for patient-related and clinical factors on performing a CRP test in relation to antibiotic prescribing.

## Results

A total of 984,149 patients redeemed at least one antibiotic prescription during the two-year period. Of these, 487,939 (49.6%) were labelled with the clinical indication RTI. Patients aged 75 years and above, with a Charlson Comorbidity Index of more than one, unemployed or on disability pension, living alone, and immigrants or descendants of immigrants had lower odds of having a CRP test performed in relation to an antibiotic prescription. Being followed in practice for a chronic condition and having CRP tests performed in the previous year were associated with higher odds of CRP testing in relation to antibiotic prescribing.

## Conclusions

Differences were observed in the use of CRP tests among subgroups of patients indicating that both sociodemographic factors and comorbidity influence the decision to use a CRP test in general practice. Potentially, this means that CRP tests are not used to an optimal extent for all groups of patients. This leaves room for improved use of CRP tests to increase diagnostic certainty and further promote rational prescribing of antibiotics.

## Keywords

General practice, Anti-Bacterial Agents, Drug Prescriptions, Diagnostic test, C-reactive Protein

## Background

Most acute respiratory tract infections (RTIs) are either non-severe or of viral origin and often the immune system is capable of controlling the infection without antibiotics. Still, these infections are frequently treated with antibiotics although it will often only add marginal benefits (1-3).

Refraining from using antibiotics in the mildly to moderately ill patients, where modest benefit can be expected, can minimise the risk of side effects for these patients and in a societal perspective reduce antibiotic resistance and costs (4-6). This approach will preserve the effectiveness of antibiotics and ensure relevant treatment of serious infections in the severely ill.

Current Danish national guidelines recommend penicillin-V as first-line treatment for RTIs, except for exacerbation of chronic obstructive pulmonary disease (COPD) for which amoxicillin is now recommended. Up until 2017 amoxicillin with clavulanic acid (co-amoxicillin) was recommended for treatment of COPD patients. For patients with penicillin allergy, either clarithromycin or roxithromycin is recommended (7). In Denmark, azithromycin is not recommended as first line treatment of RTIs in general practice.

General practitioners (GPs) are influenced by many factors when managing patients with signs and symptoms of an infection, and the C-reactive protein (CRP) test can be a useful diagnostic tool when determining if an antibiotic treatment is likely to prove beneficial or should be withheld (8-12).

All Danish GPs have access to CRP testing, and a recent Danish study showed that when GPs are provided with the result of a CRP test it constitutes an important part of the decision to prescribe or withhold antibiotics (13). Another Danish study found that CRP tests were performed in relation to about 20% of all antibiotic prescriptions issued in general practice, and differences in the use of CRP tests was observed between different antibiotic types (14).

Focussing solely on RTIs, studies have shown that CRP testing can safely reduce the use of antibiotics (15-19). Consensus exists that CRP testing cannot stand alone but should be interpreted alongside medical history, clinical findings and assessment of risk for the individual patient (20). The Danish College of General Practitioners encourages the use of CRP as a

diagnostic tool when reasonable clinical uncertainty exists. To our knowledge, no studies have systematically addressed differences in the use of CRP tests. Hence, it is unknown which factors influence GPs to perform a CRP test and whether differences are present in the use among various patient characteristics. The aim of this study was to explore patient and clinical factors associated with the use of CRP testing when prescribing antibiotics recommended for treatment of RTIs.

## Methods

This nationwide study is a retrospective cross-sectional register-based study linking Danish national registers for the adult population. Data were linked at patient-level using encrypted civil registration numbers.

### Setting

Health services in Denmark are tax-funded and medical expenditures partly subsidised. About 98% of all Danish citizens are registered with a GP. GPs are remunerated through a mixed capitation and fee-for-service system with fees for a consultation and additional fees for performing different services including CRP tests. The out-of-hour services (OOHS) are organised by the GPs in four of the five Danish Regions (21). In the fifth region the OOHS is organised by the Regional health care service.

### Study population, data sources and variables for the study

*The Danish National Prescription Registry* was used to define the population. This database contains complete information on all prescriptions redeemed by Danish residents at outpatient pharmacies in Denmark from January 1st, 1995 and onwards. The study population comprised all Danish patients aged 18 years and above redeeming prescriptions for one of the following antibiotics: penicillin-V (Anatomical Therapeutic Chemical Classification code (ATC) J01CE02), amoxicillin (ATC J01CA04), co-amoxicillin (ATC J01CR02) or roxithromycin/clarithromycin (ATC J01FA06 and J01FA09) in the project period from July 2015 to June 2017. These antibiotics were selected since they are the recommended as first line treatment for RTIs in Denmark (7). Solely prescriptions issued in general practice or OOHS were included in this study. If a patient had redeemed several antibiotic prescriptions during the project period, only information about

104 the first prescription was used for the analyses. A 14-days antibiotic free-period was required for
105 inclusion in the study. All information was linked using encrypted unique person identification
106 numbers.

107 In order to define the diagnosis for which each prescription was issued, indication codes were
108 used. These codes represent the indication stated on the prescription by the prescriber. We
109 categorised the prescriptions according to stated indication.

110 The primary outcome measure for the study was the binary variable: whether or not a CRP test
111 was performed in general practice in relation to antibiotic prescriptions. Information about the
112 performance of CRP testing was retrieved from the *Danish National Health Service Register.*
113 Since GPs report their services, including CRP tests, to the *Danish National Health Service*
114 *Register* at a weekly basis, we defined the date of the CRP test as the Wednesday in the week
115 of reporting. Therefore, a timespan of up to seven days between the performance of a CRP test
116 and redemption of prescription was allowed when defining the two measures as related.

117 A number of patient-related and clinical factors were included as covariables. GP
118 reimbursement reports obtained from the *Danish National Health Service Register* were used to
119 compute the number of CRP tests performed and number of consultations in the year before the
120 antibiotic prescription was issued, and whether the patient had follow-up consultations for one
121 or more chronic conditions the previous year. We counted tests and consultations from 14 days
122 before the prescription and one year back to avoid including CRP tests/consultations related to
123 the current event. Season of prescription was defined in two groups: October-March and April-
124 September. The number of antibiotic prescriptions in the previous 365 days before date of first
125 prescription was counted for each patient.

126 The *Danish National Patient Register* was used to quantify the burden of disease classifying
127 comorbid conditions at the patient level. The Charlson Comorbidity Index was computed using
128 the Quan 2011 method without age adjustment. Healthcare contacts in a 10 year period prior to
129 prescription were used for computing Charlson Comorbidity Index (22).

130 Socioeconomic information at the patient level were retrieved from *Statistics Denmark* and
131 linked to the prescription by encrypted unique person identification numbers. Socioeconomic
132 variables included information on gender, age groups (18-44, 45-64, 65-74, and +75 years),

133 length of education (<10 years, 10-15 years, >15 years), labour market affiliation (working,
134 pension, out of workforce/disability pension), cohabitation status (single, married/partner), and
135 ethnicity (Danish, immigrant, descendent of immigrants). For patients with missing information in
136 the year of prescription, we used information from the previous year, alternatively the following
137 year. If neither were available, the patient was assigned to the largest group.

138 From the *Service Provider Register* we retrieved speciality codes to identify GPs. We used this
139 information to take clustering at practice level into account.

### 140 Statistical analysis

141 Using descriptive statistics, we generated information on characteristics related to the
142 redeemed antibiotic prescriptions in terms of patient characteristics and clinical characteristics
143 as defined above. We used logistic regression models to estimate odds ratios (OR) with 95%
144 confidence intervals (95CI) for associations between the patient-related and clinical factors and
145 the use of CRP test in relation to prescription of antibiotics for RTIs. Univariable and
146 multivariable analyses were performed for Model 1) all prescriptions of antibiotics recommended
147 for treatment of RTIs and Model 2) the subgroup of these prescriptions with an RTI stated as
148 the indication. As sensitivity analysis, we also estimated a model including prescriptions with
149 any indications that could possibly contain an RTI, i.e. we included the indications 'against
150 infection' and missing indication. Clustering at practice level was taken into account.

151 All statistical analyses were performed using Stata 16 (23).

## 152 Results

### 153 Characteristics of patients redeeming an antibiotic prescription

154 Table 1 provides a descriptive overview of the population. A total of 984,149 individuals
155 redeemed a first-time prescription of one of the four selected antibiotic types. An RTI was stated
156 as the indication on about half of the prescriptions (49.6%). The group of potentially RTI (clinical
157 indication RTI or 'against infection' and missing indication) constituted 785.943 prescriptions
158 (79.9%) (data not shown).

159 **Table 1 Characteristics of patients redeeming antibiotic prescriptions overall and for the subgroup**

160 **of prescriptions where the GP stated RTI as indication.**

| | The four types of antibiotics recommended for RTIs (n = 984.149) | The four types of antibiotics recommended for RTIs with RTI as stated indication (n = 487,939) |
|---|---|---|
| **Patient characteristics** | | |
| *Gender* | | |
| Male | 427,735 (43.5) | 203,123 (41.6) |
| Female | 556,414 (56.5) | 284,816 (58.4) |
| *Age* | | |
| 18-44 | 377,404 (38.3) | 204,543 (41.9) |
| 45-64 | 314,242 (31.9) | 145,060 (29.7) |
| 65-74 | 157,136 (16.0) | 73,018 (15.0) |
| 75+ | 135,367 (13.8) | 65,318 (13.4) |
| *Education* | | |
| < 10 years | 205,261 (20.9) | 102,338 (21.0) |
| 10-15 years | 569,126 (57.8) | 281,636 (57.7) |
| > 15 years | 209,762 (21.3) | 103,965 (21.3) |
| *Labour market affiliation* | | |
| Working | 535,219 (54.4) | 275,368 (56.4) |
| Pension | 290,588 (29.5) | 138,098 (28.3) |
| Out of workforce, Disability pension | 158,342 (16.1) | 74,473 (15.3) |
| *Cohabitation status* | | |
| Single | 505,003 (51.3) | 252,247 (51.7) |
| Married/Partner | 479,146 (48.7) | 235,692 (48.3) |
| *Ethnicity* | | |
| Danish | 882,056 (89.6) | 438,536 (89.9) |
| Immigrant | 90,000 (9.1) | 43,266 (8.9) |
| Descendants | 12,093 (1.2) | 6,137 (1.3) |
| **Clinical characteristics** | | |
| *Comorbidity - Charlson Index* | | |
| 0 | 806,330 (81.9) | 396,184 (81.2) |
| 1 | 79,086 (8.0) | 43,998 (9.0) |
| >1 | 98,733 (10.0) | 47,757 (9.8) |
| *Chronic condition*[1] | | |
| Yes | 824,315 (83.8) | 409,481 (83.9) |
| No | 159,834 (16.2) | 78,458 (16.1) |
| *Number of consultations previous year* | | |
| 0 | 116,831 (11.9) | 57,508 (11.8) |
| 1-4 | 488,284 (49.6) | 244,483 (50.1) |
| >4 | 379,034 (38.5) | 185,948 (38.1) |
| *Number of antibiotic treatments previous year* | | |
| 0 | 737,095 (74.9) | 357,337 (73.2) |
| 1 | 179,624 (18.3) | 93,444 (19.2) |
| >1 | 67,430 (6.9) | 37,158 (7.6) |
| *Number of CRP tests previous year* | | |

| | | |
|---|---|---|
| 0 | 702,522 (71.4) | 338,392 (69.4) |
| 1 | 185,748 (18.9) | 96,543 (19.8) |
| 2- | 95,879 (9.7) | 53,004 (10.9) |
| *Prescribing indication* | | |
| Respiratory tract | 487,939 (49.6) | 487,939 (100.0) |
| Skin | 155,910 (15.8) | - |
| Other | 42,296 (4.3) | - |
| Infection | 170,882 (17.4) | - |
| Missing | 127,122 (12.9) | - |
| *Season* | | |
| October-March | 562,635 (57.2) | 308,743 (63.3) |
| April-September | 421,514 (42.8) | 179,196 (36.7) |

[1] Defined by patient being followed in practice with at least one chronic condition in the previous year.

## Factors associated with the use of CRP

Table 2 presents two multivariable models; Model 1 including all prescriptions for the four antibiotic types and Model 2 for the subgroup of prescriptions where RTI was stated as the indication on the prescription.

The multivariable model including all prescriptions within the four types of antibiotics (model 1) showed that females had slightly higher odds of having a CRP test performed in relation to antibiotic prescribing than males (OR 1.05 (95CI 1.04-1.06). Patients aged 75 years and above had lower odds for having a CRP test performed in relation to an antibiotic prescription (OR 0.82 (95CI 0.79-0.86)) compared to the youngest age group (18-44 years). A Charlson Index above 1 was associated with lower odds for CRP testing (OR 0.93 (95CI 0.91-0.95)), compared to Charlson Index 0. Contrary, being followed in general practice for one or more chronic condition showed higher odds for having a CRP test performed in relation to an antibiotic prescription, OR (1.22 (95CI 1.18-1.26). Having an education of less than 10 years, living alone, being out of workforce or at disability pension or being immigrant or descendent from immigrants were all factors associated with lower odds of having a CRP test performed in relation to an antibiotic prescription. The analyses also showed lower odds for CRP testing for patients with more than one antibiotic prescription in the previous year (OR 0.75 (95CI 0.73-0.77), but the opposite if the patient had CRP tests performed in the previous year (OR 1.78 (95CI 1.73-1.84)). Finally, seasonal differences were observed with OR 0.71 (95CI 0.70-0.72) for CRP testing in relation to prescriptions during April to September.

When restricting analyses to prescriptions with a stated RTI (model 2), we found similar trends regarding the variables as for model 1 with a few exceptions. Regarding gender, the model 2

184 showed no differences between males and females, and for comorbidity a Charlson Index of 1
185 or above was associated with lower odds of having a CRP test performed in relation to antibiotic
186 prescription.

187 Results of the univariable models and the sensitivity analysis for prescriptions with a possible
188 RTI indication (comprising prescriptions with RTI, 'against infection' or missing indication) are
189 presented in Appendix 2. The sensitivity analysis showed no major differences from model 1.

190 **Table 2 Factors associated with the use of a CRP test in relation to antibiotic prescribing**

| | Model 1<br>Multivariable model for the four types of antibiotics recommended for RTIs<br>(N = 984,149) | Model 2<br>Multivariable model for the four types of antibiotics recommended for RTIs with RTI as stated indication<br>(N = 487,939) |
|---|---|---|
| **Patient characteristics** | OR (95% CI) | OR (95% CI) |
| Male | 1 | 1 |
| Female | 1.05 (1.04-1.06) | 1.00 (0.98-1.01) |
| 18-44 | 1 | 1 |
| 45-64 | 1.02 (1.00-1.03) | 1.19 (1.17-1.22) |
| 65-74 | 1.05 (1.01-1.08) | 1.30 (1.24-1.35) |
| 75+ | 0.82 (0.79-0.86) | 0.91 (0.86-0.96) |
| Education < 10 years | 1 | 1 |
| Education 10-15 years | 1.05 (1.03-1.07) | 1.10 (1.08-1.12) |
| Education > 15 years | 1.04 (1.02-1.07) | 1.13 (1.10-1.17) |
| Working | 1 | 1 |
| Pension | 1.00 (0.98-1.03) | 1.01 (0.97-1.05) |
| Out of workforce or disability pension | 0.84 (0.83-0.85) | 0.90 (0.88-0.92) |
| Single | 1 | 1 |
| Married/Partner | 1.08 (1.07-1.10) | 1.07 (1.05-1.09) |
| Danish | 1 | 1 |
| Immigrant | 0.91 (0.88-0.95) | 0.92 (0.89-0.96) |
| Descendant of immigrants | 0.90 (0.84-0.96) | 0.91 (0.84-0.98) |
| **Clinical characteristics** | | |
| Charlson 0 | 1 | 1 |
| Charlson 1 | 1.07 (1.05-1.09) | 0.92 (0.90-0.95) |
| Charlson >1 | 0.93 (0.91-0.95) | 0.87 (0.84-0.90) |
| No chronic conditions | 1 | 1 |
| Chronic conditions[1] | 1.22 (1.18-1.26) | 1.24 (1.19-1.29) |
| 0 contacts previous year | 1 | 1 |
| 1-4 contacts previous year | 0.99 (0.98-1.01) | 1.03 (1.01-1.05) |
| >4 contacts previous year | 1.03 (1.00-1.05) | 1.13 (1.10-1.17) |
| 0 antibiotic treatments previous year | 1 | 1 |
| 1 antibiotic treatment previous year | 0.91 (0.90-0.93) | 0.83 (0.82-0.85) |
| >1 antibiotic treatment previous year | 0.75 (0.73-0.77) | 0.64 (0.62-0.66) |
| 0 CRP previous year | 1 | 1 |
| 1 CRP previous year | 1.33 (1.30-1.36) | 1.23 (1.20-1.27) |
| >1 CRP previous year | 1.78 (1.73-1.84) | 1.58 (1.52-1.64) |
| October-March | 1 | 1 |
| April-September | 0.71 (0.70-0.72) | 0.93 (0.92-0.95) |

191 [1] Defined by patient being followed in practice with at least one chronic condition in the previous year.

192 ## Discussion

193 ### Main findings

194 This nationwide population-based study included 984,149 individuals who had received an
195 antibiotic prescription during the 2-year study period. A total of 49.6% of the prescriptions had
196 RTI stated as the indication. Differences in the use of CRP tests, when prescribing antibiotics,
197 was identified both in relation to patient and clinical characteristics.

198 Both models showed that the odds of having a CRP test performed when prescribed antibiotics
199 for an RTI was lower for the elderly (75 years and above), and for patients with comorbidity
200 indicated by the Charlson Comorbidity Index > 1. One of the reasons for this finding might be
201 that clinical and medical history and the risk of complications in this age group carry more
202 weight. Hence, GPs may not find CRP testing necessary when deciding to prescribe antibiotics
203 for patients who are more vulnerable due to age and/or comorbidity. Furthermore, a proportion
204 of these patients may be too old or frail to be able to attend general practice and will need home
205 visits with no access to POC tests. On the other hand, these groups are also more vulnerable to
206 side-effects of antibiotics, meaning that diagnostic certainty should be prioritised. Being followed
207 in general practice for one or more chronic condition was associated with higher odds of having
208 a CRP test performed in relation to an antibiotic prescription for an RTI. In contrast, we find
209 lower odds of CRP testing with higher comorbidity score, indicating that these two measures
210 might assess different aspects. Patients with more than four consultations in practice in the
211 previous year had also higher odds for a CRP test, which may be explained by the fact that
212 these patients are well-known in practice and are more inclined to visit general practice for a
213 test.

214 CRP tests are also less used for individuals out of workforce or on disability pension, living
215 alone, immigrants and descendants of immigrants. These findings suggest that some groups of
216 patients are treated differently with no evident differences in terms of risk of complications.

217 Having more than one CRP test performed in the previous year was a predictor of having a
218 CRP test performed in relation to an antibiotic prescription, indicating that there is a group of
219 patients, where CRP tests are more often used. Antibiotic treatment in the previous year
220 reduced the chances of having a CRP test performed. This could be well-reasoned, but it could
221 also reflect a tendency of repeating previous treatment without awareness about a potentially

new situation. This could indicate that this is an area where CRP tests are not used to the optimal extent.

## Strengths and limitations of the study

This study is based on nationwide registers, recognised for their high validity and ability to cover the entire Danish population, hereby providing a large data material.

However, some limitations must be considered when interpreting the results. The study used the Danish National Prescription Registry which gave us access to redeemed prescriptions. Prescriptions issued, but not redeemed, were not accessible. However, a previous Danish study have found that primary non-adherence for antibiotics is only 6.5% (24).

Another Danish study found that 32% of antibiotic prescriptions had a missing indication (16). The indications used in this study are the ones stated by the GPs on the prescriptions and only 13% were missing. We attempted to account for this by estimating two models, one with all prescriptions and one with the subgroup of prescriptions with RTI as stated indication. The multivariable models were adjusted for all covariables, since these variables were selected based on hypothesis of influencing the main outcome. We did not take time trends into account, since the study period only covered two years, and as a recent study found that frequency of use of CRP tests did not change over the study period (14).

The database was restricted to patients who redeemed an antibiotic recommended for RTIs. Hence, we were not able to assess patients for whom the GP chose to perform a CRP test but did not prescribe antibiotics. For future studies to further understanding of the diagnostic process it could be relevant to study the way GPs use CRP tests also for patients where the GP did not prescribe antibiotics. In this study it was not possible to distinguish OOHS from daytime in general practice. Different diagnostic approaches must be expected in general practice and in OOHS, where the physician does not know the patient and has access to fewer diagnostic tools.

The study uses temporal links between CRP tests and antibiotic prescriptions. Data do not confirm whether it is the same GP who performed the test and issued the prescription. In addition, we allowed a timespan of up to 7 days between CRP test and prescription. This

250 approach was necessary since the use of CRP tests are reported on a weekly basis. However,
251 we consider this timespan clinically appropriate and would not expect it to constitute a large
252 limitation to the study.

253 **Findings in relation to existing knowledge**

254 Antibiotic prescribing can be influenced by many factors such as patients' medical history;
255 comorbidity; clinical examination; and the result of a CRP test (13, 15, 25). We found
256 differences in the use of CRP tests among different groups of patients. Odds for using CRP
257 tests were lower for the elderly and patients with comorbidities (defined by Charlson Score
258 above 1). Previous studies have shown that initial clinical judgement carry a high diagnostic
259 value (26, 27). Perhaps the clinical judgement plays a larger role with this group of patients,
260 including assessment of probability of benefits of antibiotic use and potential risk of
261 complications to the illness. However, the odds of having a CRP test performed when
262 prescribed antibiotics for an RTI are also lower when the patient is out of workforce or on
263 disability pension, living alone, an immigrant or descendant of immigrants. This correlates with
264 previous studies from other areas showing that there is a social inequality in diagnosing in
265 health care (28, 29). The results of the present study indicate that GPs are prescribing
266 antibiotics for elderly and socially marginalised using the CRP test as a diagnostic aid to a
267 lesser extent. This could constitute a risk of irrational use of antibiotics including risk of side-
268 effects and selection for resistant bacteria.

269 We found that having a CRP performed in the previous year was associated with increased
270 odds of having a CRP test in relation to an antibiotic prescription. This finding is in line with
271 another study, which found that there are differences in the use of diagnostic tests between
272 practices in the range of use of diagnostic tests (30). Whether this is related to the patient or
273 more likely explained by differences in GPs' use of tests is not possible to say from the present
274 study but could be further explored in future studies.

275 **Implications**

276 This study discovered differences in the use of CRP tests among different patient groups.
277 Socially deprived patients had lower odds of having a CRP test performed in relation to an
278 antibiotic prescription for an RTI. Further studies should attempt to get a deeper knowledge of

why patients are handled differently, with a special focus on socioeconomic inequality. The influence of GP factors on the decision to use a CRP test was not assessed in this study, however this angle could also be an important topic for future studies.

Furthermore, the study findings might call for clearer guidelines for GPs on how and when to apply CRP tests in clinical practice. The existing evidence on when to use the CRP test could be implemented more explicitly in the clinical recommendations for treatment of RTIs. In a broader perspective, it must be expected that a wider selection of POC tests will be available in the future.

## Conclusion

Differences were observed in the use of CRP tests, among subgroups of patients treated with antibiotics for an RTI, indicating that patients with different socioeconomic characteristics are handled differently. Potentially, this means that CRP is not used to the optimal extent for all groups of patients and leaves room for optimising diagnostic certainty and further promote rational prescribing of antibiotics.

## List of abbreviations

CRP: C-reactive protein

95CI: 95% confidence interval

GP: General practitioner

OR: Odds ratio

RTI: Respiratory tract infection

## Declarations

### Ethics approval and consent to participate

Complying with European data protection rules, the University of Southern Denmark registered the data processing activities regarding this project (registration number 10.053). Data were obtained from Danish national registries, and the study was approved by the Danish National Health Data Board (FSEID-00004071) and the Danish Patient Safety Authority (3-3013-2095/1).

According to Danish law a strictly register-based study needs no approval from The Regional Committees on Health Research Ethics for Southern Denmark, neither from the participants. All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Consent to participate: Not applicable.

## Consent for publication

Not applicable.

## Availability of data and materials

The data that support the findings of this study are available from Statistics Denmark, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Statistics Denmark.

## Competing interests

The authors declare no competing interests.

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## Authors' contributions

RVS, MPH, USJ, LBP, RMA, SW and DEJ took part in developing the project idea. RVS, SW and DEJ developed the analysis plan. Statistical analysis was performed by RVS. RVS drafted the manuscript. RVS, MPH, USJ, LBP, RMA, SW and DEJ read and approved the final manuscript.

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## Authors' information (optional)

Not applicable.

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