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ORIGINAL RESEARCH ARTICLE

# Temporal and regional differences in the incidence of hospital-diagnosed endometriosis: a Danish population-based study

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## Abstract

**Introduction:** Due to diagnostic challenges, normalization of symptoms and an overall lack of awareness among both patients and physicians, endometriosis is an underdiagnosed disease. This can result in delayed treatment and potentially worsening of the disease. Despite initiatives, such as patients' support organizations and specialized endometriosis referral centers, differences in awareness, socioeconomic factors and lifestyle, combined with varying distances to specialized referral centers, could result in regional differences in the degree of underdiagnosing. This study aims to explore temporal and regional variations in the incidence of endometriosis based on the Danish hospital discharge register, and shed light on the degree of underdiagnosing of endometriosis in Denmark.

**Material and methods:** This registry-based cohort study included all women aged 15–55 living in Denmark from 1990–2017. Participants were identified through the Danish Civil Registration system and endometriosis diagnoses received at a hospital were obtained from the Danish National Patient Registry. Incidence rates of diagnosed endometriosis were calculated for each year of the study period and for each municipality in Denmark. A Cox regression analysis, stratified by calendar time and adjusted for ethnic origin, household composition, highest educational level and family socioeconomic status, was performed to estimate the association between residence and likelihood of receiving a hospital-based diagnosis of endometriosis.

**Results:** The nationwide incidence rate of hospital-diagnosed endometriosis was 7.89 (95% confidence interval [CI] 7.80–7.99) per 10 000 person-years and the prevalence in 2017 was 1.63%. The results showed an overall increase in the incidence of diagnosed endometriosis of 46.8% (95% CI 32.9–62.2) during the study period and also displayed significant regional differences. After adjustments, women living in northern Jutland had the highest probability of receiving a hospital-based diagnosis of endometriosis (hazard ratio 1.13, 95% CI 1.09–1.18), whereas women living in northern Zealand had the lowest probability (hazard ratio 0.63, 95% CI 0.60–0.67) compared with eastern Jutland. These regional differences have become more evident over time.

**Abbreviations:** CI, confidence interval; DCRS, Danish Civil Registration System; DNPR, Danish National Patient Registry; IR, incidence rates.

**Conclusions:** Our results reveal significant regional differences in the incidence of hospital-diagnosed endometriosis, suggesting that a significant number of women may be left behind without a diagnosis. Further studies are needed to assess the underlying reasons for the significant regional differences.

**KEYWORDS**
endometriosis, epidemiology, diagnosis, incidence, diagnostic delay, cohort study, demographics

## 1 | INTRODUCTION

Delayed or neglected diagnosis remains a challenge for those with symptomatic endometriosis[1] because delayed treatment may result in a worsening of the disease. Available data indicate that both patient and physician factors are to blame.[1–3] Women endure their symptoms because of embarrassment and an inaccurate perception of normal vs abnormal pain,[1,2] which prevents them from seeking medical attention.[3] At the medical level, pelvic pain is often normalized or dismissed by physicians and the symptoms associated with endometriosis are often nonspecific, which challenges the diagnostic process.[1–3] Other factors such as race, educational level and socioeconomic status have also been suggested as predictors for receiving an endometriosis diagnosis.[4–8] Hence, a combination of many different factors can be responsible for the underdiagnosing of a potentially large number of women with symptomatic endometriosis.

Actions taken to remedy this situation include the formation of patient support organizations and the establishment of specialist endometriosis referral centers within the public healthcare system. This should ideally result in increased awareness and faster diagnosing and thereby increase the incidence of diagnosed endometriosis.[9] However, geographic, cultural and socioeconomic differences might influence the impact of such initiatives.

This study aimed to explore temporal and regional variations in the incidence of hospital-diagnosed endometriosis, and to shed light on the degree of underdiagnosing of symptomatic endometriosis in Denmark.

**Key message**

Our study shows a considerable increase in the incidence of hospital-diagnosed endometriosis in Denmark over time and reveals significant regional differences, which suggests varying degrees of underdiagnosing depending on the region of residence.

## 2 | MATERIAL AND METHODS

### 2.1 | Study population and design

In this combined registry-based cohort study and population time trend analysis, the study population consisted of all women aged 15–55 living in Denmark at some point between 1 January 1990 and 31 December 2017. All participants were identified through the Danish Civil Registration System (DCRS), which contains personal data on everyone with a residence permit living in Denmark. These were followed for varying lengths of time during the study period from 1990 to 2017. Demographic, socioeconomic and hospital data from different registries were merged using the unique personal identification number which is assigned to everyone in Denmark at birth or immigration.

### 2.2 | Residential information

Residential information on all participants was obtained from DCRS for each year of the study period. Residence was defined as municipality of residence for the descriptive analysis (98 municipalities) and divided into 11 regions for the comparative analysis. The residential information was handled dynamically during the follow-up period, ie the status could change if a participant moved from one municipality or region to another.

### 2.3 | Diagnosis of endometriosis

All Danish citizens have free access to the healthcare system, with direct access to the general practitioner and free choice of public hospitals across regional borders. The general practitioner is the first contact in the healthcare system. When specialists (e.g., gynecologists) or hospital care is needed, referral from the general practitioner is required. Hospital referral is needed to get a surgically verified diagnosis.[10,11]

Data regarding diagnoses of endometriosis were obtained from the Danish National Patient Registry (DNPR), which contains information on all in- and outpatients discharged from Danish hospitals since 1977. Since 2002, data has also been recorded from private hospitals, though the majority of endometriosis patients are referred to and managed within the public healthcare system (97.51% in 2007 and 98.75% in 2017).[12]

The outcome was defined as the first primary diagnosis of endometriosis, identified with the ICD-8 codes 62 530 and 62 532–62 539 (before 1994) and ICD-10 codes DN801-809 (from 1994 onwards). This includes all diagnoses regardless of histologic or surgical history. Diagnoses of adenomyosis were not included. The positive and negative predictive value and the sensitivity for the diagnosis of endometriosis using ICD-8 codes in the DNPR has been estimated to be 95.1%, 89.3% and 45.8%, respectively.[13,14]

Both main (reason for contact) and subsidiary (present but not the main reason for contact) diagnoses of endometriosis were included, and the date of diagnosis was defined as the hospital admission date for the first endometriosis diagnosis.

Additionally, information on all histologically verified diagnoses of endometriosis was acquired from the Danish Pathology Data Bank.

## 2.4 | Covariates

Additional information on date of birth, ethnic origin (Danish, immigrant or descendant of an immigrant), and household composition (single woman, couples or other) was obtained from DCRS. Information on the highest educational level (primary, upper secondary, vocational, short higher education, medium-long higher education, long higher education), and family socioeconomic status (self-employed/executive, employed, on social benefits, student, other) was obtained from Statistics Denmark. The family socioeconomic status is determined by the occupational position of the adult with the highest income in the family. No clinical covariates were considered due to the exploratory, descriptive goals of the study.

## 2.5 | Statistical analyses

### 2.5.1 | Descriptive analysis

Women aged 15–55 and living in Denmark, with no prior recorded diagnosis of endometriosis, were followed from 1 January 1990. Girls who turned 15 during the study period entered the study on their 15th birthday. The women were followed until receiving their first hospital-based diagnosis of endometriosis, their 55th birthday, death, emigration or end of follow-up, whichever came first. Women aged over 15 who immigrated to Denmark during the study period, were excluded.

Nationwide incidence rates (IR) were calculated for each year of the study period, 1990–2017, both unstratified and stratified by age group. The geographic distribution of the incidence of endometriosis in Denmark was described by calculating IRs for each municipality for the entire period from 1990 to 2017. To assess potential differences in IRs of endometriosis depending on age, and to account for potential regional differences in the age distribution, the IRs for each municipality were further stratified into four age groups (15–25, 25–35, 35–45 and 45–55). Based on the development in hospital-diagnosed endometriosis over time, the IRs were also stratified by calendar time (1990–1999, 2000–2009 and 2010–2017).

As a subanalysis, IRs for each municipality were also calculated restricting the outcome to include only histologically verified diagnoses of endometriosis, using the date of histological diagnosis as the index date.

### 2.5.2 | Comparative analysis

To estimate the association between residence and the likelihood of a hospital-based diagnosis of endometriosis, both crude and adjusted Cox regression analyses were performed, with age as the underlying time scale and region of residence as the explanatory variable. The analyses were stratified by calendar time and adjusted for the following potential confounders: ethnic origin, household composition, highest educational level and family socioeconomic status. Information on household composition, highest educational level and family socioeconomic status was updated yearly and treated as time-dependent variables. Taking into account the wide age distribution in the study population, the covariate for the highest educational level was represented by the parents' highest educational level if the woman was aged 15–25. Information about family socioeconomic status was not reported in the first 4 years of the study period. Thus, to enable adjustment for this covariate, the information recorded for the first time in 1994, was used in the previous years from 1990–1993 as well, under the assumption that socioeconomic status does not tend to change rapidly or drastically over short time intervals in Denmark. The region eastern Jutland was used as the reference in all the analyses.

All statistical analyses were performed using Stata/MP 15 (Stata Corporation, College Station, Texas).

## 2.6 | Ethical approval

The study was approved by the Danish Data Protection Agency under the Aarhus University comment agreement (j.number 2015-57-0002) and Aarhus University j.number 2016–051-000001, sequential number 1242 (Date: 27 September 2018). According to Danish legislation, ethical approval of registry studies is not required.

# 3 | RESULTS

From a total of 2 188 720 women (33 633 161 person-years) fulfilling the inclusion criteria, there were 26 605 women with a first diagnosis of endometriosis based on hospital admissions in 1990–2017 in Denmark, corresponding to an IR of 7.89 (95% confidence interval [CI] 7.80–7.99) per 10 000 person years). The prevalence of endometriosis diagnosed at a hospital in 2017 was 1.63%.

Demographic and socioeconomic characteristics of the study participants in the 11 regions of Denmark are presented for the year 2017 in Table 1. The proportion of several factors differed between regions. For example, the proportion of immigrants varied between regions, as did the proportion of women with a higher education (≥5 years), single women, women on social security benefits and students.

The nationwide IRs, calculated for each year of the study period 1990–2017, showed an overall increase of 46.8% (95% CI 32.9–62.2) over time, with an IR of 5.46 in 1990 (95% CI 5.07–5.87) and an IR of 8.01 in 2017 (95% CI 7.50–8.56) (Figure 1). A rise in IR was especially noted in the years around 2000, which continued until 2005. In the following years, the IR decreased but remained elevated compared with the period before 2000. The increase in IR occurred among all age groups, except for those aged 45–55, for whom the IR seemed fairly constant.

The IRs for each municipality in Denmark for the entire study period of 1990–2017, ranged between 4.98 and 12.37 and displayed an uneven geographic distribution of hospital-based endometriosis diagnoses with a clear tendency towards higher IRs in the northern and eastern parts of Jutland. When stratified into age groups, the range of IRs differed between groups, but displayed geographic distributions similar to those found in the overall analysis (Figure S1).

Approximately 60% of the diagnoses were histologically verified ($n$ = 15 881). The subanalysis, restricted to histologically verified diagnosis, displayed a geographic distribution similar to the analyses using all hospital diagnoses, but with a tendency towards increased IRs in areas surrounding Copenhagen and eastern Zealand (Figure S2).

The IRs stratified by period showed a change in the geographic distribution of hospital-based endometriosis diagnoses over time (Figure 2). In the first period of 1990–1999, the geographic

**TABLE 1** Demographic and socioeconomic characteristics of women living in different regions of Denmark in 2017

| | Regions of residence | | | | |
|---|---|---|---|---|---|
| **Covariates** | **CPH** | **GCPH** | **NZ** | **BO** | **EZ** |
| *n* (%) | 162 990 (14.23) | 101 023 (8.82) | 85 073 (7.43) | 7048 (0.62) | 50 346 (4.40) |
| Age, mean (SD) | 32.77 (10.77) | 34.93 (12.61) | 36.15 (13.15) | 37.01 (13.06) | 35.94 (12.80) |
| Origin % | | | | | |
| Danish | 90.69 | 87.47 | 94.76 | 98.30 | 94.77 |
| Immigrant | 3.67 | 4.63 | 2.39 | 1.22 | 2.30 |
| Descendant of immigrant | 5.64 | 7.89 | 2.85 | 0.48 | 2.94 |
| Missing, *n* | 44 | 13 | 17 | <10 | <10 |
| Highest educational level % | | | | | |
| Primary school | 8.57 | 13.01 | 10.23 | 15.78 | 10.33 |
| Upper secondary school | 7.59 | 5.99 | 5.55 | 3.87 | 5.49 |
| Vocational school | 21.25 | 34.88 | 34.01 | 48.12 | 40.26 |
| Short further education (2 y) | 5.01 | 5.99 | 6.51 | 3.64 | 7.17 |
| Medium-long further education (3–4 y) | 30.75 | 23.50 | 26.39 | 23.88 | 24.46 |
| Long further education (≥5 y) | 26.83 | 16.64 | 17.29 | 4.71 | 12.29 |
| Missing, *n* | 714 | 484 | 325 | 16 | 168 |
| House type, % | | | | | |
| Single woman | 29.88 | 25.32 | 19.46 | 24.84 | 20.65 |
| Couples | 47.10 | 59.55 | 64.50 | 64.22 | 64.96 |
| Other | 23.02 | 15.13 | 16.04 | 10.94 | 14.38 |
| Socioeconomic status, % | | | | | |
| Self-employed/executives | 7.29 | 9.44 | 12.57 | 9.90 | 11.16 |
| Employed | 68.56 | 73.55 | 74.35 | 70.79 | 75.16 |
| Social security benefits | 7.92 | 9.33 | 7.45 | 13.37 | 7.54 |
| Students | 14.53 | 6.26 | 4.29 | 4.79 | 4.95 |
| Other | 1.70 | 1.44 | 1.34 | 1.14 | 1.18 |
| Missing, *n* | 1120 | 425 | 307 | 19 | 167 |

Abbreviations: CPH, Copenhagen; GCPH. Greater Copenhagen; NZ, Northern Zealand; BO, Bornholm; EZ, Eastern Zealand; WSZ, Western and Southern Zealand; Funen (F), SJ, Southern Jutland; EJ, Eastern Jutland; WJ, Western Jutland; NJ, Northern Jutland.

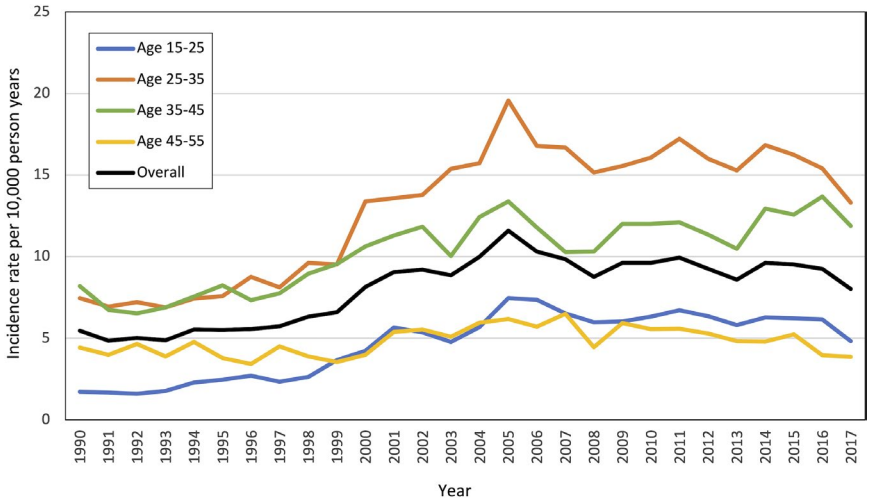


**FIGURE 1** Incidence rates of diagnosed endometriosis per 10 000 person years for each calendar year of the study period 1990–2017, divided into age groups

| WSZ | FU | SJ | EJ | WJ | NJ | Total |
|---|---|---|---|---|---|---|
| 116 973 (10.21) | 99 577 (8.69) | 139 835 (12.21) | 180 631 (15.77) | 83 864 (7.32) | 118 047 (10.31) | 1 145 407 (100) |
| 35.97 (12.71) | 34.71 (12.53) | 35.10 (12.71) | 34.01 (12.25) | 35.11 (12.73) | 34.90 (12.53) | 34.74 (12.42) |
| 96.41 | 94.91 | 95.75 | 94.93 | 97.09 | 97.27 | 94.32 |
| 1.82 | 2.50 | 2.40 | 2.45 | 1.66 | 1.66 | 2.59 |
| 1.77 | 2.58 | 1.85 | 2.63 | 1.26 | 1.07 | 3.09 |
| 13 | 19 | 24 | 24 | 10 | 10 | 183 |
| 17.12 | 13.69 | 15.25 | 11.23 | 14.41 | 14.21 | 12.77 |
| 4.05 | 4.54 | 4.37 | 5.35 | 4.73 | 4.43 | 5.27 |
| 44.00 | 39.90 | 42.78 | 36.01 | 43.19 | 41.84 | 37.03 |
| 5.49 | 5.46 | 5.62 | 6.44 | 6.18 | 5.40 | 5.81 |
| 24.03 | 27.37 | 25.86 | 27.62 | 26.05 | 26.07 | 26.57 |
| 5.30 | 9.04 | 6.12 | 13.35 | 5.44 | 8.05 | 12.55 |
| 533 | 356 | 589 | 549 | 297 | 435 | 4466 |
| 23.18 | 23.74 | 22.00 | 22.09 | 20.05 | 22.07 | 23.33 |
| 62.13 | 63.37 | 68.33 | 63.40 | 71.10 | 67.81 | 62.38 |
| 14.69 | 12.89 | 9.67 | 14.51 | 8.85 | 10.12 | 14.28 |
| 8.23 | 8.25 | 9.70 | 8.78 | 10.13 | 8.87 | 9.14 |
| 72.16 | 68.87 | 72.98 | 69.75 | 73.65 | 71.73 | 71.56 |
| 12.74 | 12.19 | 10.77 | 10.20 | 10.48 | 10.47 | 10.05 |
| 5.04 | 9.11 | 5.25 | 10.17 | 4.68 | 7.62 | 7.86 |
| 1.82 | 1.59 | 1.30 | 1.09 | 1.06 | 1.32 | 1.40 |
| 341 | 345 | 517 | 786 | 326 | 368 | 4721 |

differences in Denmark were small, with only slightly higher IRs in the northern part of Jutland compared with the rest of the country. In the following period of 2000–2009, these differences were accentuated, with increased IRs in especially northern and eastern Jutland. In the last period of 2010–2017, the higher IRs in northern Jutland persisted, now accompanied by higher IRs on Funen as well, whereas the IRs in eastern Jutland decreased.

The regression analysis comparing the regional incidence of hospital-diagnosed endometriosis for the entire study period of 1990–2017, showed that women living in northern Jutland had the highest probability of receiving a hospital-based diagnosis of endometriosis, with a 13% higher likelihood (hazard ratio 1.13, 95% CI 1.09, 1.18) compared with residents in eastern Jutland (Figure 3). All the other regions had lower likelihoods compared with eastern Jutland.

When the regression analysis was stratified by calendar time, Northern Jutland continued to have the highest incidence in all three periods (Figure 4). All other regions display a consistently lower incidence, except for eastern Jutland, which had an incidence equivalent to Northern Jutland in 2000–2009.

The Cox regression analysis, restricted to histologically verified diagnoses, showed similar results for the last two calendar periods (2000–2017), but in the first period (1990–1999) the results were more inconsistent (Figure S3).

## 4 | DISCUSSION

Our results showed a considerable increase in the nationwide incidence of hospital-diagnosed endometriosis during the last two decades of the study period. The results also displayed significant regional differences in the incidence, which remained when adjusting for sociodemographic factors and after restricting results to histologically verified diagnoses. This suggests varying degrees of underdiagnosing depending on the region of residence.

The estimated prevalence of endometriosis varies widely according to published studies based on various study populations.[15] Based on multiple epidemiological studies, the general assumption is that endometriosis affects up to 10% of women of reproductive age.[16–18] If this assumption is correct, the prevalence of hospital-diagnosed endometriosis found in this study (1.63%) seems low, suggesting a large number of undiagnosed cases in Denmark. Yet, recent studies have found similar results (1.82% and 0.9%, respectively).[19,20]

Most previous epidemiological studies have estimated IRs ranging from 4.5 to 35 per 10 000 person years, which agrees with the nationwide IR of 7.89 per 10 000 person years found in the present study.[6,8,21–24] The large variation in incidence estimates partly reflects different ways of outcome assessment as well as different methodologic strategies. However, the increase in incidence over time seen in this study does not correspond with the development seen in other countries, including other Nordic countries.[6,21–23,25] A study from Iceland including only visually confirmed diagnoses, found an increasing incidence from 1991 to 1997, followed by a drop from 1998 to 2000.[23] A Finnish study found a decreasing incidence from 1996 to 2012, in line with results from Sweden in 1996–2004.[21,25] Differences in the development in incidence over time could partly reflect different study-periods, different outcome definitions as well as differences in diagnostic procedures.

The Danish increase in incidence started in the years around 2000, which coincided approximately with the formation of a patient support organization in 1997 and the establishment of specialist referral centers for endometriosis in 2001. Our design does not allow for causal interpretations but the results may reflect that these initiatives led to an increased awareness of the symptoms of endometriosis among the general population as well as within the medical profession. Another possible explanation could be the improvement in diagnostic methods over the years. However, current evidence about the accuracy of these methods does not appear to support this theory.[26]

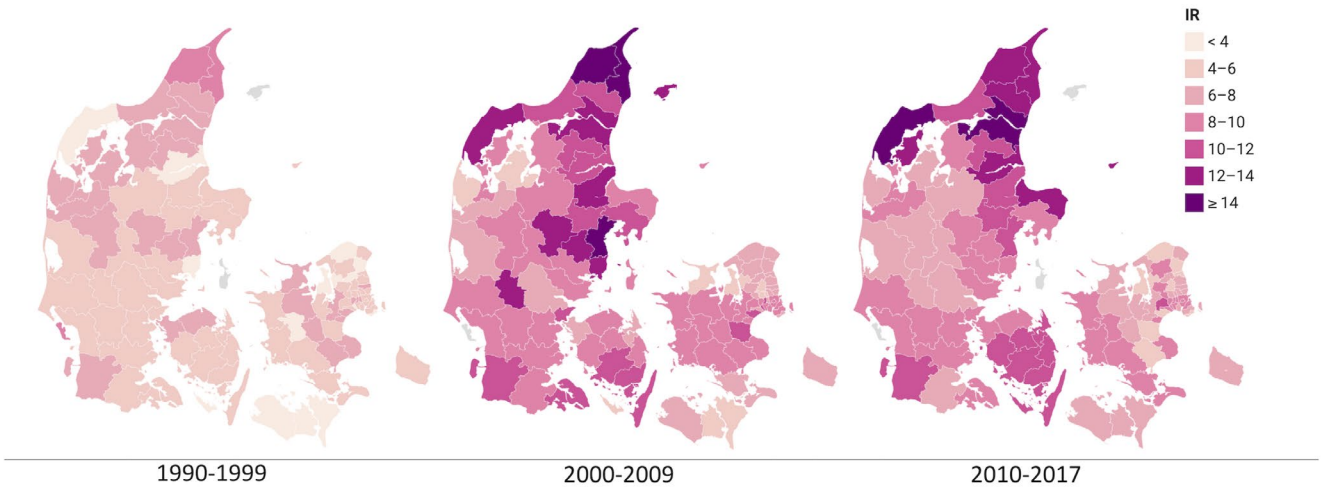


FIGURE 2 Incidence rates of diagnosed endometriosis per 10 000 person years in each municipality of Denmark in three different periods among women aged 15–55. Grey areas have <5 cases of endometriosis

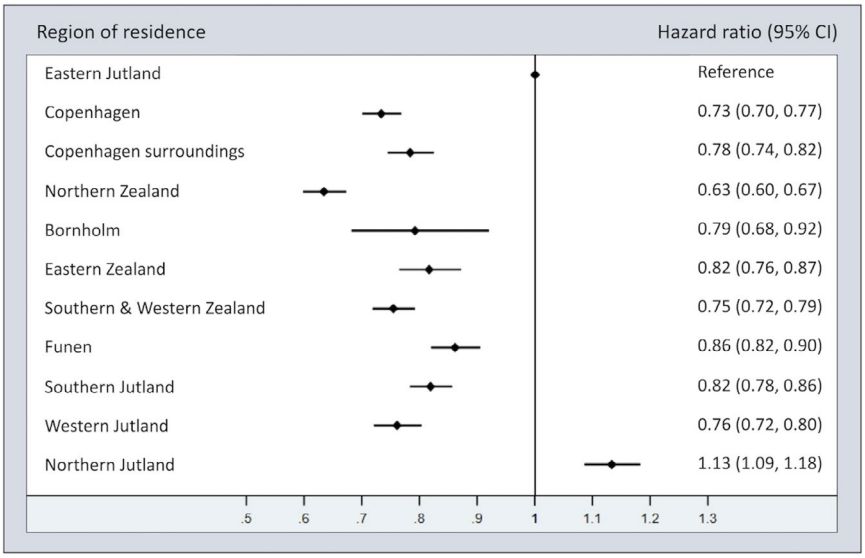


**FIGURE 3** Hazard ratios of a diagnosis of endometriosis for each region of Denmark compared with Eastern Jutland. Adjusted for ethnic origin, household composition, highest educational level and family socioeconomic status

In western Denmark, the highest incidence rates were seen in the municipalities surrounding the referral center, and also in municipalities in northern Jutland and on Funen. Regional differences in awareness influenced by cultural factors, differences in the tendency to seek medical attention and attitudes of healthcare professionals represent potential explanations. In addition, the distribution of risk factors associated with endometriosis (e.g., body mass index, age at menarche, etc.) could vary between regions and contribute to the regional differences.[27,28] A few studies have previously found noticeable regional differences in the incidence and prevalence of endometriosis in north-western Italy and France, respectively. These studies discuss the potential influence of different pollutants and genetic factors as a possible explanation for the regional differences.[6,20] Although environmental or genetic factors cannot be ruled out as a potential explanation for the present results, the regional differences found in the present study are more likely to reflect structural differences and differences in awareness across regions. In contrast to the results for western Denmark, a generally lower incidence of hospital-diagnosed endometriosis was seen in eastern Denmark, and only moderate or no changes in incidence were seen over time. This could indicate a higher degree of underdiagnosing or perhaps a lower prevalence of potential risk factors in that part of the country. It could, however, also be explained by differences in referral routines, since many patients with pelvic pain in this area are referred to specialists in private practices instead of hospitals. Diagnosis and management by specialists in these clinics are covered financially by the public system, but data on diagnosis are not reported to DNPR. The number of private gynecologic practices differs greatly between eastern and western Denmark, e.g., there were seven times as many private specialists per 100 000 inhabitants in Copenhagen than in northern Jutland in 2015.[29] A large number of women with a diagnosis of endometriosis, made in private practices in eastern Denmark, may therefore be unknown to this study. However, severe cases of endometriosis would still be expected to be referred, diagnosed and treated surgically at hospital level, but the results only changed slightly when restricted to histologically verified diagnosis. Our results, therefore, support the findings of significant regional differences in incidence, thus suggesting the existence of a relatively large group of women with undiagnosed endometriosis in eastern and some parts of western Denmark. Revision of diagnostic and referral practices could be needed to further improve diagnosis (or diagnosis pickup) of endometriosis.

The major strength of our study is the registry-based platform, with a large nationwide cohort and almost complete follow-up of from 1990 to 2017. Information about residence was obtained from DCRS, and information about endometriosis diagnoses was obtained from DNPR. In both registries, information is collected routinely and prospectively, thus avoiding recall bias. The data in the DCRS are virtually complete and are generally of high accuracy. Previous validation data have shown a relatively high positive and negative predictive value of the ICD-8 codes, but since these validation data are older, they do not cover ICD-10 codes and were estimated among women undergoing gynecologic surgery, the PPV and NPV are not necessarily transferrable to this study. Some degree of non-differential misclassification must be expected.[13,14,30] Another strength is the adjustment for various sociodemographic variables in the regression analysis.[4,5] Furthermore, the potential confounding effect of both age and calendar time is taken into account through the design of the regression model. The objective of this study was not to draw causal inference and estimate an association completely free from confounding, but rather to describe the geographic differences and eliminate the effect of known confounders. Geographic location is presumably not the direct cause of high or low incidence of hospital-diagnosed endometriosis, but rather unknown covariates associated with the specific location (e.g., awareness-level, distance to hospital, medical history, environmental factors). Future studies should investigate the role of these confounders and mediators more closely. Finally, the results are strengthened by the analysis based solely on histologically verified diagnoses, which reduces some of the potential bias from the uneven distribution of gynecologic private practices.

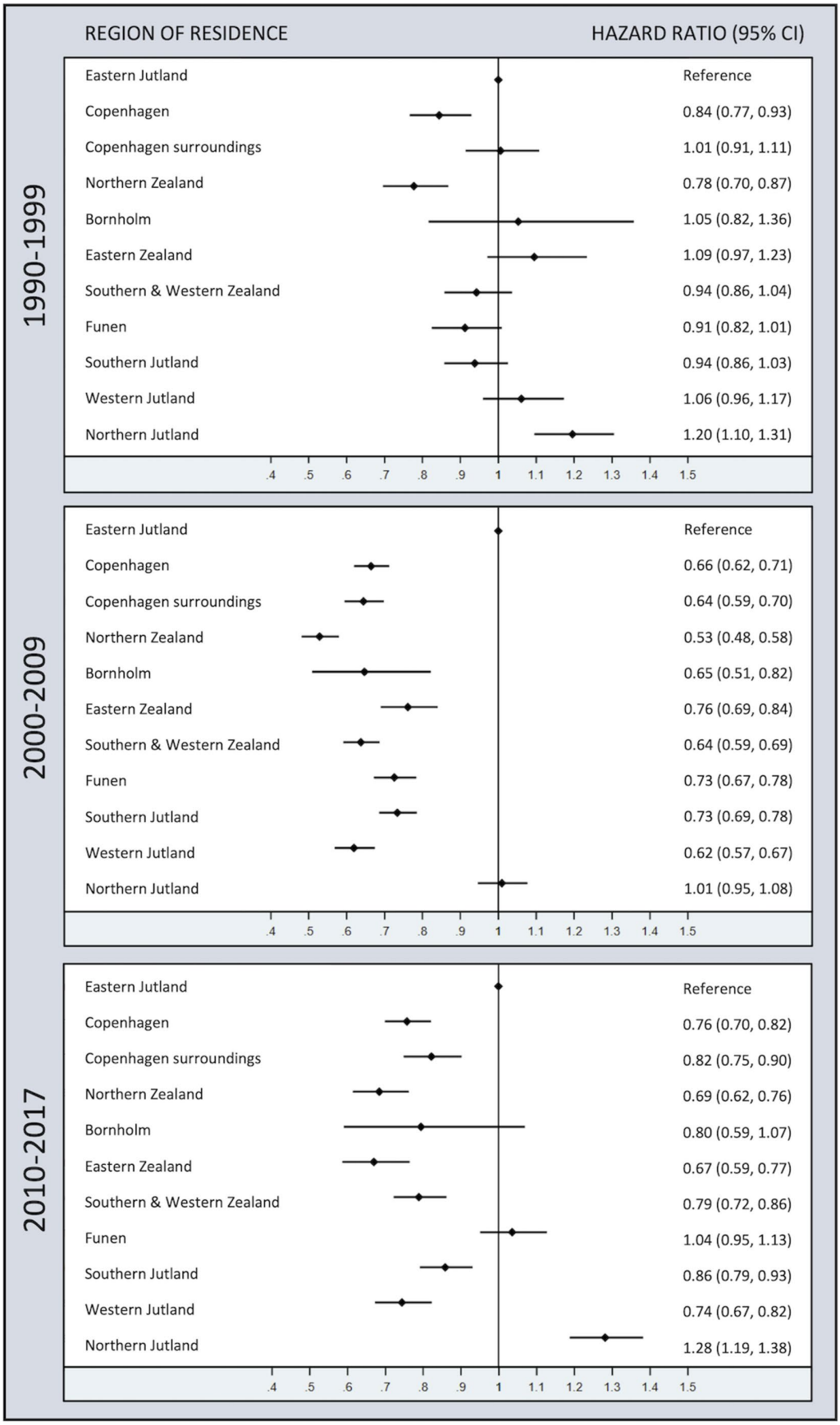


**FIGURE 4** Hazard ratios for a diagnosis of endometriosis for each region in Denmark compared with Eastern Jutland in three different periods. Adjusted for ethnic origin, household composition, highest educational level and family socioeconomic status

The main limitation of our study is the lack of information on diagnoses made outside of hospital settings, and the uneven distribution of private gynecologists in Denmark presents a possibility for differentiated misclassification of the outcome status, especially in eastern Denmark.

## 5 | CONCLUSION

Our study found an overall increase in the incidence of hospital-diagnosed endometriosis from 1990 to 2017, but with significant regional differences in this incidence. There are many potential explanations for the geographic differences in incidence, but our data suggest that a significant number of women may be left behind without diagnosis in some regions of Denmark. Further studies are needed to determine the causes and consequences of regional differences in the diagnosis of endometriosis.

### CONFLICT OF INTEREST

There are no conflicts of interest relating to this work.

### AUTHOR CONTRIBUTIONS

Study concept and design: LRHI, AF and DR. Data curation and management: LRHI, AM and DR. Formal analyses and data interpretation: LRHI, SNH, DR, LH, MN and KEH. Draft manuscript: LRHI. Critical discussion, review, editing and final approval: All authors.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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