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Identification of potential hotspot areas and impact of urbanisation

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Geographical and ecological analyses of multiple myeloma in Denmark: Identification of potential hotspot areas and impact of urbanisation

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Abstract

Background: The aetiology of multiple myeloma (MM) is unknown but various environmental exposures are suspected as risk factors. We present the first paper analysing the geographical distribution of MM in Denmark at the municipal level to investigate variations that could be explained by environmental exposures.

Methods: Patients diagnosed with MM in Denmark during 2005–2020 were identified from nationwide registries and grouped into the 98 Danish municipalities based on residence. The age- and sex-standardised incidence rate (SIR) of each municipality was compared to the national incidence in a funnel plot with 95% control limits. Differences in SIRs of rural, suburban, and urban areas were evaluated with incidence rate ratios.

Results: In total, 5243 MM patients were included. Overall, we found a heterogeneous geographical distribution of MM and a potential hotspot in southern Denmark. This hotspot contains three municipalities with SIRs above the 95% control limit assuming considerably higher rate of MM compared to the national incidence rate. A significant higher SIR was found in rural areas compared to urban areas.

Conclusion: The geographical distribution of MM in Denmark indicates that the risk of developing MM depends on place of residence probably due to environmental factors.

KEYWORDS

disease hotspot, epidemiology, incidence, multiple myeloma, spatial analysis

Novelty statements

1. What is the NEW aspect of your work? To our knowledge, this is the most detailed study of the geographical distribution of multiple myeloma in an entire country due to small geographical groupings with adjustments for both age and sex.
2. What is the CENTRAL finding of your work? We found a heterogeneous geographical distribution with a hotspot area and higher incidence in rural areas compared to urban indicating that the risk of multiple myeloma depends on place of residence probably due to environmental factors.
3. What is (or could be) the SPECIFIC clinical relevance of your work? "Why me and could it have been prevented?" is a common question in the consultation room; nevertheless, our findings encourage future studies to clarify the aetiology focusing on risk factors in the environment, particularly in rural areas and the identified hotspot area.

1 | INTRODUCTION

Multiple myeloma (MM) is a clonal plasma cell proliferative disorder in the bone marrow and the second most common haematological malignancy. Knowledge of aetiology may pave the way for prevention and thereby reducing the incidence of MM in the future.[1,2]

The aetiology of MM is largely unknown, but risk factors as older age, positive family history, male sex, Afro-American ethnicity, and some polygenetic factors are acknowledged; however, the exact causal mechanisms are undetermined.[1,3,4] Various environmental exposures such as pesticides and benzene have been suspected as risk factors but have mostly been investigated in an occupational context.[3,4] Previous studies have examined the geographical distribution of MM in selected countries or areas. Some propose that the spatial heterogeneity in incidence rate may be explained by the degree of urbanisation due to environmental factors, but reports are conflicting and often limited because of large geographical groupings or lack of adjustment for the demographic in the background population.[5–9]

Denmark has a population of about six million inhabitants and is organised into five regions and 98 municipalities. Taking the small area of the country into account, 98 zones allow a detailed investigation of the spatial distribution of MM. Furthermore, comprehensive data on population demographics can be accessed through the Danish Civil Registration System.[10] Few studies have investigated the geographical distribution of MM in an entire country and none in such detailed level as the Danish municipalities allow. The overall aim of this study was to present how MM is geographically distributed in Denmark. Furthermore, we evaluated the incidence rate of MM by degree of urbanisation.

2 | MATERIALS AND METHODS

2.1 | Data source

All citizens in Denmark are registered in the Danish Civil Registration System (CRS) and assigned with a personal identification number (CPR number).[10] The CPR number enables linkage between various registers, specifically allowing us to link a patient's place of residence with health conditions from clinical registries such as the population-based Danish National Multiple Myeloma Registry (DMMR). The data in DMMR have been described in detail and validated by Gimsing et al.[11] In brief, hospitals and haematological centres in Denmark are obligated to register patients with plasma cell dyscrasia to DMMR and the completeness is almost 100%. The registry contains clinical information including date of diagnosis, disease characteristics, and date of treatment. From DMMR we identified Danish residents diagnosed with MM, while the municipality of residence was extracted from CRS. We chose the municipal residence of patients to be the residence 6 months before the date of diagnosis. Population

demographics from 2014 of the entire country and each municipality were obtained from Statistics Denmark.[12]

Municipalities were categorised by Statistics Denmark in 2012 using Eurostat's Degree of Urbanisation classification (DEGURBA).[13,14] DEGURBA differentiates between 'Cities' (densely populated areas), 'Towns and suburbs' (intermediate density areas), and 'Rural' (thinly populated areas) areas, which in the present study are termed urban, suburban, and rural, respectively.

Coordinates describing municipal boundaries for choropleth mapping were extracted from the Danish Administrative Geographical Division register which is available online.[15]

2.2 | Study population

The study cohort included patients fulfilling the following criteria: (1) diagnosed with symptomatic MM in Denmark during January 1st, 2005, and December 31st, 2020. (2) Permanent residence in Denmark at 6 months before diagnosis. Patients diagnosed with smouldering MM (SMM), monoclonal gammopathy of undetermined significance, amyloid light-chain amyloidosis, POEMS syndrome, solitary plasmacytoma, primary plasma cell leukaemia, and other plasma cell dyscrasias were not included in this study. As patients diagnosed with SMM and symptomatic MM were registered under the same code in DMMR between 2005 and 2018, we distinguished between SMM and symptomatic MM using the following criteria: Patients without treatment or progression (death within 90 days from date of diagnosis) throughout the study period were identified as SMM. Patients who had deselected treatment were categorised as symptomatic MM. In the following, symptomatic MM is termed MM.[16]

2.3 | Statistical methods

Baseline characteristics of MM patients were presented as percentage for categorical variables (sex, age group, M-protein type, stage, and year of diagnosis), while age as a continuous variable was summarised by median and interquartile range (IQR). All incidence rates were estimated as the number of MM cases in the study period divided by the 2014 Danish population multiplied by 15 years (to approximate person-years). All incidence rates were presented as per 100 000 person-years. Crude incidence rates were supplied with 95% confidence intervals (CIs) based on Byar's method.[17] To account for different demographics in the municipalities, standardised incidence rates (SIRs) were calculated by direct standardisation with respect to sex and age using the age groups <60, 60–64, 65–69, 70–74, 75–79, ≥80 years and the 2014 Danish population as reference population.[18,19] The estimated SIRs were equipped with 95% CIs based on the method by Tiwari et al.[19] Confidentiality rules in Denmark prescribe exclusion of municipalities with <5 cases in tables and figures; however, the direct method required exclusion of municipalities with <10 cases. The SIRs were visualised in funnel plots using the national incidence of MM as benchmark with 95% and 99.95% control limits.[20] If the SIR was above the 95% control limit it was considerably higher than the national incidence. The second control limit (99.95%) was based on Bonferroni correction to limit the challenge of multiple testing, as we conducted the test across all municipalities. The spatial distribution of SIRs was visualised in choropleth maps.

The SIRs were calculated for rural, suburban, and urban areas according to the above principles of standardisation. To evaluate the impact of the degree of urbanisation, the differences of SIRs were analysed with incidence rate ratios (IRRs) with 95% CIs based on the method by Tiwari et al.[19] The difference were considered significant if the CIs did not contain the value of one.

In secondary analyses, we explored the bias due to relocations in residence as the data quality allowed examination at least 25 years prior to date of diagnosis for all the included patients. This was presented as percentage of MM patients who have lived in the same municipality throughout the period.

All data were pseudo-anonymised and stored on a secured server governed by Statistics Denmark. Statistical analyses were carried out in R version 4.0.3 (2020-10-10).[21] In Denmark, register-based studies conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law. However, the study was approved by the data responsible institute (North Denmark Region—Approval number: 2021-034 and 2021-056) in accordance with the General Data Protection Regulation (GDPR).

3 | RESULTS

3.1 | Baseline characteristics

In total, 6176 patients were diagnosed with MM in Denmark during the 2005–2020 period. We excluded 21 MM patients without Danish residence and 912 patients categorised as SMM leaving 5243 patients for the study population. The median age at diagnosis for males was 71 years (IQR: 63–78) and 72 years (IQR: 64–79) for females. Baseline characteristics of the study population are shown in Table 1.

3.2 | Geographical distribution of MM in Denmark

The SIRs of MM cases were analysed in 95 municipalities as two municipalities were excluded due to confidentiality rules and direct standardisation excluded one municipality due to less than 10 cases. The national incidence rate of MM was 6.2 per 100 000 person-years in Denmark. As can be seen in the funnel plot and the map in Figure 1, the SIRs of four municipalities were above the control limit (95%) assuming substantial higher incidence rate of MM compared to the national incidence rate. These four municipalities were Vejen, Vejle, Horsens, and Albertslund and had a SIR per 100 000 person-years of 9.6 (95% CI: 7.4–12.2), 7.5 (95% CI: 6.2–9.0), 7.7 (95% CI: 6.2–9.4), and 8.7 (95% CI: 5.8–12.6), respectively. Three out of the four municipalities (Vejen, Vejle, and Horsens) were located almost next to each other in southern Denmark. The lowest SIRs were found

TABLE 1 Baseline characteristics of multiple myeloma patients and the national crude incidence rates between 2005 and 2020.

Characteristics	Patients *N* (%)	Population[a] *N* (%)	Incidence rate[b] (95% CI)
Total	5243 (100)	5 627 000 (100)	6.2 (6.0–6.4)
Age group (years)			
<60	853 (16.3)	4 263 000 (75.8)	1.3 (1.2–1.4)
60–64	634 (12.1)	338 000 (6.0)	12.5 (11.6–13.5)
65–69	824 (15.7)	356 000 (6.3)	15.4 (14.4–16.5)
70–74	957 (18.3)	255 000 (4.5)	25.0 (23.4–26.6)
75–79	860 (16.4)	180 000 (3.2)	31.8 (29.7–34.0)
≥80	1115 (21.3)	235 000 (4.2)	31.6 (29.8–33.6)
Sex			
Female	2307 (44.0)	2 835 000 (50.4)	5.4 (5.2–5.7)
Male	2936 (56.0)	2 792 000 (49.6)	7.0 (6.8–7.3)
Type of M-protein[c]			
FLC	496 (9.5)	-	-
IgA	1076 (20.5)	-	-
IgD	31 (0.6)	-	-
IgG	2847 (54.3)	-	-
IgM	31 (0.6)	-	-
More than one type	140 (2.7)	-	-
Non-specific	15 (0.3)	-	-
ISS stage[d]			
1	1130 (21.6)	-	-
2	1679 (32.0)	-	-
3	1654 (31.5)	-	-
Year of diagnosis			
2005–2010	1755 (33.5)	-	-
2011–2015	1611 (30.7)	-	-
2016–2020	1877 (35.8)	-	-

Abbreviations: CI, confidence intervals; FLC, Free light chain; ISS stage, the International Staging System.
[a]Population refers to the Danish population in 2014 and is shown as thousands.
[b]The national incidence rate per 100 000 person-years.
[c]Due to confidentiality rules the exact number of patients with IgE type (<5 patients) could not be shown in the table. Patients without recordings of M-protein type and patients with IgE accounted for 607 (11.6%) patients.
[d]ISS stage could not be categorized for 780 (14.9%) patients.

in eastern Denmark, except for Albertslund which is a suburb of the capital Copenhagen (København). The SIRs of Vejen, Vejle, Horsens, and Albertslund were above the 95% control limit with 1.41, 0.09, 0.12, and 0.14 per 100 000 person-years, respectively. The most southern of the four municipalities, Vejen, had the highest SIR and was almost above the very restrictive control limit of 99.95% with a difference of only 0.07 per 100 000 person-years.

As can be seen in Table 2, the SIR of urban, suburban, and rural areas in Denmark was 5.9 (95% CI: 5.6–6.2), 6.3 (95% CI: 6.0–6.6), and 6.4 (95% CI: 6.1–6.7) per 100 000 person-years, respectively. We found rural areas to have a slight but statistically significant higher SIR of 8% (95% CI: 1.01–1.16) compared to urban areas. The SIR in suburban areas was 7% (95% CI: 1.00–1.15) higher than urban areas but not statistically significant. Two out of the four high-incidence municipalities (Vejen and Vejle) were categorised as rural, while Horsens and Albertslund were categorised as suburban and urban, respectively.

Characteristics (name, crude incidence rate, SIR, degree of urbanisation) of each municipality are accessible in Table S1. Figure S1 gives a geographical overview of the distribution of rural, suburban, and urban municipalities. Location and name of each municipality are accessible when comparing Table S1 and Figure S1 by the assigned number. Figure S2 shows the spatial distribution of the municipalities based on crude incidence rates. Figure S3 shows that only 20% of MM patients have changed municipal residence up to 25 years before diagnosis.

4 | DISCUSSION

In this nationwide study, we evaluated the SIRs of MM in 95 municipalities in Denmark to explore environmental risk factors for MM. We found four municipalities with SIRs above the control limit of 95%,

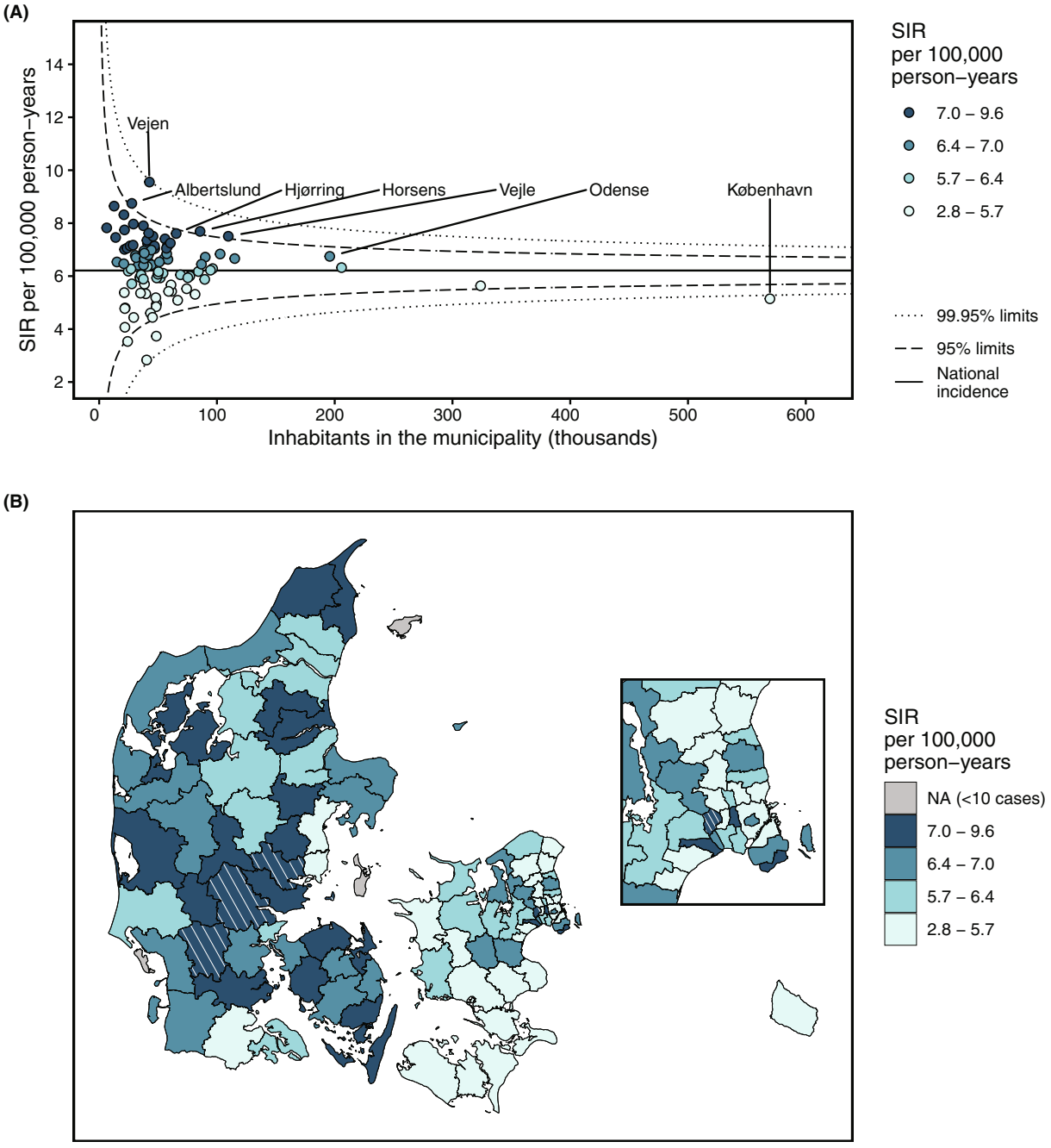

FIGURE 1 The distribution of age- and sex-standardised incidence rates (SIRs) of multiple myeloma among Danish municipalities. (A) Funnel plot of SIR of each municipality expressed as point estimate. The x-axis expresses the population size within each municipality. The horizontal line is the national incidence (6.2). The dashed lines represent the 99.95% (Bonferroni-corrected limits) and the 95% control limits, respectively. (B) The geographical distribution of multiple myeloma based on SIRs. The shaded areas indicate municipalities with higher SIR than the upper limit of the 95% control limit. Numbers in the colour range are determined as the smallest incidence, 1st quartile, the median incidence, 3rd quartile, and the highest incidence of all SIRs.

assuming a considerably higher incidence rate of MM in these areas compared to the national incidence rate in Denmark. The highest municipal SIR of MM was marginals from being above the control limit of 99.95%. Furthermore, we found approximately 8% higher SIR of MM in rural areas compared to urban areas. Few studies have investigated the geographical distribution of MM in an entire country. To our knowledge, this is the most detailed study considering the relatively small sizes of Danish municipalities and at the same time taking the demographics into account.[6,7,9]

The geographical distribution of MM revealed a substantial heterogeneous pattern, as the lowest SIRs were found in eastern Denmark and the highest SIRs mainly in southern Denmark (Figure 1). Three municipalities with substantial higher SIRs were located almost next to each other supporting the idea of a hotspot or clustering area.

TABLE 2 Distribution of the Danish municipalities and SIRs of multiple myeloma patients by degree of urbanisation (urban, suburban, and rural areas).

Degree of municipality	Municipalities *N*	Population[a] *N* (%)	SIR[b] (95% CI)	IRR (95% CI)
Urban	18	1 921 000 (34.1)	5.9 (5.6–6.2)	Ref
Suburban	35	1 821 000 (32.4)	6.3 (6.0–6.6)	1.07 (1.00–1.15)
Rural	45	1 886 000 (33.5)	6.4 (6.1–6.7)	1.08* (1.01–1.16)

Abbreviations: CI, confidence intervals; IRR, incidence rate ratio; SIR, age- and sex-standardised incidence rate.
*Significant (CI does not contain the value of one).
[a]Population refers to the Danish population in 2014 and is shown as thousands.
[b]per 100.000 person-years.

Further studies are needed to investigate potential environmental factors related to this hotspot.

Several suggestions have been raised in the literature and some assume that agricultural employment and pesticides are a risk factor for MM.[3,4] This contributes to a theory of higher incidence in rural areas. We analysed the difference between rural, suburban, and urban areas and found a higher SIR of MM in rural areas compared to urban areas. Our finding agrees with Tsang et al. who investigated the MM distribution in Canada. The Canadian study is comprehensive, but no adjustments for background demographics were made.[9] Sneyd et al. investigated the distribution of MM patients in New Zealand and found both highest and lowest incidence rates in rural areas, but the geographic areas in their study were large compared to Danish municipalities.[7] By contrast, Rajabli et al. found that MM was most common in urban areas, but the analysis was only based on 124 cases of MM from the Golestan province of Iran.[8] Some suggests air pollution as a risk factor in urban areas; however, a significantly negative correlation between MM incidence rates and areas with high air concentration of pollutants as black carbon and fine particles were found by Kamath et al. based on analysis of the 34 neighbourhoods in New York City.[5]

In a preventive context, type 1 errors are preferred to type 2 errors; therefore, municipalities were assessed by a 95% control limit, despite the risk of false discoveries due to multiple testing. Nevertheless, Bonferroni correction was made in addition for comparison but must be considered an overly restrictive limit as the SIR are most likely correlated due to the neighbouring municipalities made with man-made boundaries. Afro-American ethnicity is stated as an established risk factor in literature based on the US population.[1,2] However, no adjustment for race were made in this study due to the small number of immigrants and relatives from Africa in Denmark.[12,22] This study has neither adjusted for possible inheritance because it is not immediately possible to distinguish between genetic factors and the fact that relatives probably have been exposed to the same environment throughout life. Although a combination of both is not inconceivable. As in other studies on this topic, the potential bias due to different diagnostic practices may occur. We attempted to eliminate this by exclusion of SMM patients; however, there may always appear a small but mentionable difference in how to diagnostically obtain the basis for assessing the myeloma-defining events.[1,16] If a nationwide screening program will be implemented in the future as a result of the iStopMM study, this type of study will be able to include SMM patients due to more homogeneity in diagnostic practice.[23] Possible environmental exposure need time to evolve onset of a malignancy, therefore, change of residence may dilute our findings. We found that only 20% of MM patients have changed municipal residence up to 25 years prior to MM diagnosis. We chose a cross-sectional date 6 months prior to diagnosis to accommodate that people may move due to poorer health at the time of diagnosis. In addition, environmental factors may vary over time, and we investigated the cumulative incidence of MM during the 15 years. Thereby, we may miss possible environmental risk factors that only occurred part-time of the study period. To overcome this limitation, shorter time periods are needed; however, this will introduce lack of power when investigating a relatively rare cancer as MM. The strengths of our study are the nationwide study design with complete information regarding place of residence thanks to the CRS. The health system in Denmark is based on taxation giving free access to health services, thereby decreasing the impact of socioeconomic factors. We analysed SIRs taking both sex and age into account to eliminate the demographic difference between municipalities. We estimated the SIRs of MM in relatively small geographic areas making our results more precise regarding potential permanent environmental risk factors.

In conclusion, we found a MM hotspot area of neighbouring municipalities in southern Denmark containing three out of four municipalities with a substantial higher SIR of symptomatic MM compared to the national incidence rate. One of these municipalities is particularly suspicious as its SIR was almost above the overly restrictive control limit of 99.95%. Presumably, environmental factors related to the residence are not solely to blame, considering the many variables that could interact with people over time. However, these findings support the possibility that the residential environment may have a role to play in the development of myeloma and demands further research on environmental risk factors. The slight but statistically significant higher SIR in rural areas asks for further research on risk factors associated with rurality, while Danish municipalities may cover too large an area.

AUTHOR CONTRIBUTIONS

Marianne Tang Severinsen, Lars Børty Nielsen, Henrik Gregersen, Heidi Søgaard Christensen, Martin Bøgsted, and Lise Dueholm Bertelsen conceptualized, and designed the study. Henrik Gregersen, Robert Schou Pedersen, Anja Klostergaard, Brian Iversen Schnack, Per

Trøllund Pedersen, Niels Abildgaard, Emil Hermansen, and Annette Juul Vangsted facilitated the data collection. Lise Dueholm Bertelsen, Lars Børty Nielsen, Heidi Søgaard Christensen, and Martin Bøgsted conducted the statistical analysis. Lise Dueholm Bertelsen, Lars Børty Nielsen, Heidi Søgaard Christensen, Martin Bøgsted, Henrik Gregersen, and Marianne Tang Severinsen analysed and interpreted the data. Lise Dueholm Bertelsen wrote the manuscript. All authors made a critical revision and approved the final manuscript.

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CONFLICT OF INTEREST

Annette Juul Vangsted has received honoraria from Celgene. All the other authors have none to declare.

DATA AVAILABILITY STATEMENT

Research data from Statistics Denmark cannot be shared according to Danish law.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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