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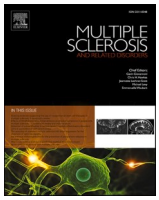

Original article

Neonatal outcomes in women with Multiple Sclerosis – Influence of disease activity: A Danish nationwide cohort study

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ABSTRACT

Background: Maternal Multiple Sclerosis (MS) has been associated with an increased risk of adverse birth outcomes. We hypothesized that active disease during conception and pregnancy plays an important role in this context, which this study aims to address.

Methods: We used the Danish registers to conduct a nationwide cohort study. Information on maternal disease activity during pregnancy was retrieved using proxies from the linked registers (hospitalization, magnetic resonance imaging of the brain, and use of systemic corticosteroids during pregnancy). Neonates, exposed in utero to maternal disease activity constituted the exposed cohort and the unexposed cohort constituted neonates without in utero exposure to maternal disease activity. The examined outcomes were preterm birth, small for gestational age, low 5-minute Apgar score, and major congenital anomalies. In logistic regression models we estimated the odds ratios (OR) with adjustment for confounders such as maternal age, comorbidities, parity, smoking, calendar year of birth, and disease-modifying treatment.

Results: Among the study population of 2492 children of mothers with MS we identified 273 (11 %) neonates exposed to maternal disease activity during pregnancy, and 2219 (89 %) neonates without exposure to disease activity. The adjusted odds ratios (aOR) for preterm birth, small for gestational age, low 5-minute Apgar score, and major congenital anomalies among children born to women with disease activity during pregnancy were 0.92 (95 % confidence interval (95 % CI) 0.53–1.60), aOR 1.19 (95 % CI 0.62–2.26), aOR 2.57 (95 % CI 0.93–7.15) and aOR 0.93 (95 % CI 0.48–1.83), respectively.

Conclusions: Women with MS having disease activity during pregnancy did not have a statistically significantly increased risk of adverse neonatal outcomes compared to women with MS without disease activity, which is overall reassuring results. We believe, that this will be useful knowledge for patients and clinicians in planning a pregnancy and preparing a birth plan.

1. Introduction

Multiple Sclerosis (MS) is the most common progressive neurological disease among young adults. The majority of patients who are diagnosed with MS are women aged between 20 and 40 years and this coincides with the peak of reproduction for many new young families. Choosing to have children has become more common among women with MS in the last two decades (Jolving et al., 2016; Villaverde-Gonzalez, 2022), and this raises concerns about the potential influence of MS during pregnancy and birth. In order to counsel these women as best as possible

Abbreviations: MS, Multiple Sclerosis; OR, odds ratio; aOR, adjusted odds ratio; CPR, civil-personal-registration; DMT, disease-modifying treatment; ICD, International Classification of Diseases; ATC, Anatomical therapeutic chemical classification.

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through pregnancy, this has led to an increasing number of studies in the area.

The etiology of MS is not fully understood, but it is widely accepted that a component of autoimmunity and abnormal expression of cytokines is involved in the chronic inflammatory nature of the disease (Palle et al., 2017). Clinical manifestations of MS depend on which areas of the central nervous system are affected, but especially the loss of muscle coordination, weakness and fatigue, and affection of the smooth muscles could potentially have a great impact on pregnancy and birth. Furthermore, a healthy pregnancy requires precisely coordinated communications between the mother and the fetus, where immune cells and cytokines signaling pathways participate as important mediators. However, when dysregulated or inappropriately expressed as in MS, they may interrupt fetal and placental development (Yockey and Iwasaki, 2018).

Maternal MS has been associated with an increased risk of adverse neonatal outcomes in some previous cohort studies. Statistical significantly increased risk of small for gestational age has been found in 3 previous studies (Andersen et al., 2021; Chen et al., 2009; Fink et al., 2023), persistent after adjustment for confounders. Also, an increased risk of preterm birth has been found in women with MS based on data from claim- and insurance data, but also recently with nationwide register data (Chen et al., 2009; Fink et al., 2023; MacDonald et al., 2019).

In general, it is difficult to separate the effects of disease activity, the use of disease-modifying treatments and the impact of the underlying disease, when analyzing the risk of adverse neonatal outcomes (Andersen et al., 2023; Krysko et al., 2023). We found only one study by Fink et al. (2023) addressing the influence of disease activity on adverse pregnancy and birth outcomes. Most recently literature shows that the majority (67 %) of women with MS conceiving have suboptimal disease control (Langer-Gould et al., 2020; Krysko et al., 2023). It is documented that women suspending treatment with Natalizumab prior to pregnancy have higher risk of disease activity during pregnancy and postpartum compared to women who suspended Rituximab prior to pregnancy or women without disease-modifying treatment prior to pregnancy (Razaz et al., 2020).

We aimed to study adverse neonatal outcomes in women with disease activity during pregnancy. It is highly relevant to study this subgroup of women with MS with the more severe disease course. Adverse neonatal outcomes such as preterm birth, small for gestational age, low Apgar score, and congenital anomalies are important outcomes because they are strong predictors of short- and long-term child morbidity and mortality (Barker, 2007; Gillette et al., 2022; Meas et al., 2010; Razaz et al., 2022). Using information from the nationwide Danish health registries we applied proxy variables of maternal disease activity during pregnancy (hospitalization, magnetic resonance imaging of the brain, and use of systemic corticosteroids during pregnancy) in order to establish a cohort of neonates exposed to disease activity.

2. Methods

2.1. Setting

In Denmark, all citizens have free access to a tax-supported national healthcare secure system. The Danish population of about 5.8 million inhabitants has a ten-digit civil registration number (CPR) assigned at birth and immigration that is used across all Danish health registers for valid record linkage of each contact at an individual level. All health activities are mandatorily registered and not for research use as the main purpose, which gives a unique possibility to conduct nationwide population-based cohort studies.

2.2. Data

We established a study population of all childbirths by women with MS from 1998 to 2018 by using the following registers; the Danish National Patient Register, the Danish Medical Birth Register, the Danish Multiple Sclerosis Treatment Registry, and the Danish National Prescription Register. Identification of the women with MS and their childbirths derived from the Danish National Patient Register and the Danish Medical Birth Register by linkage of data via the CPR number. We used the Danish Multiple Sclerosis Treatment Registry to confirm the MS diagnosis and to trace disease-modifying treatment (DMT) courses within 120 days prior to conception and during the pregnancy period. The Danish Multiple Sclerosis Treatment Registry was established in 1996 and contains prospectively collected clinical data of all MS patients receiving DMT from all Danish departments of neurology at treatment initiation, after 3 months, and further on every 6th month in relation to clinical visits (Mason et al., 2012). The Danish National Patient Register has collected information on all hospital discharges in Denmark since 1977 and since 1994 all outpatient visits. The register contains diagnoses and procedures performed, the date of admission and discharge, and information on the location of the hospital and department (Schmidt et al., 2015). In 1994, the registration of diagnoses was changed from the Danish version of the International Classification of Diseases in the 8th revision (ICD-8) to ICD-10. From the Danish National Patient Register, we obtained information on the first affirmative diagnosis of MS (ICD-8: "340″ and ICD-10 "G.35″) (Boesen et al., 2018; Mason et al., 2012) before conception. Accurate censoring at death and emigration was based on the CPR system (Schmidt et al., 2014). Furthermore, we used the Danish National Prescription Register where data since 1995 has been collected on all redeemed prescriptions of medication in any pharmacy based on CPR number including information on time and place of redemption (Kildemoes et al., 2011; Pottegard et al., 2017). All medications in the register are classified according to the Anatomical Therapeutic Chemical Classification (ATC) system. We used this register to trace redeemed systemic corticosteroid prescriptions 30 days prior to conception or during pregnancy according to the ATC codes: "H02AB02" (dexamethasone), "H02AB04" (methylprednisolone), "H02AB06" (prednisolone), "H02AB07" (prednisone), and "H02AB09" (hydrocortisone). From the National Prescription Register we also retrieved information on MS-specific immuno-suppressive – and disease-modifying treatments together with information from the above-mentioned Danish Multiple Sclerosis Treatment Registry.

The Danish Medical Birth Register includes information on all births in Denmark since 1973, and links mother and child through the CPR number, and it includes data on the mother, the father, pregnancy-related background information and information on birth outcomes. The date of conception was based on information from the Danish Medical Birth Register according to ultrasound measurements of the gestational age (Bliddal et al., 2018; Knudsen and Olsen, 1998; Kristensen et al., 1996).

2.3. Study population

The study population comprised all singleton live births by women with a primary or secondary diagnosis of MS before the time of conception from 1st January 1998 to 31st of December 2018. From the Danish Multiple Sclerosis Treatment Registry we confirmed MS diagnosis. We used a 1-year follow up on all children according to diagnoses of congenital anomalies.

2.4. The exposed and unexposed cohorts

We decided to use three parameters to establish the cohort of women with MS experiencing "disease activity-related events" during their pregnancy. A recent study using the Danish nationwide registers documented that combinations of parameters such as hospitalizations, corticosteroid treatments, and radiological examinations have a good predictive ability to detect both severe disease activity but also mild-to-moderate inflammatory flare-ups not requiring in-hospital treatment (Burisch et al., 2021). Therefore, the exposed cohort constituted

neonates born to women with MS having disease activity during pregnancy defined according to one or more of the three following parameters: (1) a prescription of systemic corticosteroids 30 days prior to conception or during pregnancy, (2) hospitalizations during pregnancy, including only those who had an MS diagnostic code as the primary reason for the hospitalization, or (3) patients who were examined with MRI scan of the brain during pregnancy. To ensure that we did not overlook other indicators for disease activity during pregnancy we also searched for intravenous corticosteroid administration in our dataset, but no patients had these procedure codes during pregnancy.

The unexposed cohort comprised neonates born to women with MS who did not have indicators of disease activity during pregnancy.

2.5. Data on covariates

From the Danish Medical Birth Register we extracted data on maternal age at childbirth (continuous), maternal smoking status at conception (yes/no), parity (0, 1+), mode of delivery (vaginal birth or caesarian section), calendar year of childbirth distributed into categories ([1998–2003], [2004–2008], [2009–2013], and [2014–2018]), maternal body mass index (BMI) when entering the pregnancy (underweight [< 18.5 kg/m^2], normal weight [18.5– 24.9 kg/m^2], overweight [25.0–29.9 kg/m^2], and obese [> 30 kg/m^2]). Information on BMI is available in the register from 2005. From the Danish Multiple Sclerosis Treatment Registry, we confirmed MS diagnosis and extracted information on disease length (period from first affirmative diagnosis of MS and until conception) and DMT 120 days prior to conception or during pregnancy until birth (see Supplementary – S1 for a list of ATC-codes). From the Danish National Patient Register, we obtained information on maternal comorbidity 10 years prior to conception according to Charlson's comorbidity index (CCI) (Charlson et al., 1987). Diagnoses of comorbidity were divided into a two-level index of no comorbidity and some comorbidity (0, 1+). Information on maternal pregnancy complications was retrieved since these diagnoses are associated with adverse child outcomes (Billionnet et al., 2017; Bokslag et al., 2016); gestational diabetes (ICD O.244), and preeclampsia (ICD O.14).

2.6. Outcome ascertainment

The fetal outcomes of interest included preterm birth (defined by birth before 37 completed gestational weeks, small for gestational age estimated according to the Marsal et al. algorithm that is below -2SD conforming to gestational age and sex (Marsal et al., 1996), and 5-minute Apgar score < 7 (Ehrenstein et al., 2009). Major congenital anomalies diagnosed within the first year of life were identified with ICD-codes from chapter Q (congenital malformations, deformations and chromosomal abnormalities) supplied with P.350 Congenital Rubella syndrome, P.351 Congenital Cytomegalovirus Infection, P.371 Congenital Toxoplasmosis Syndrome, D.18.1A Cystic hygroma, D.21.5 Sacral teratoma, and D.82.1 Pharyngeal pouch syndrome in line with the Danish translation of EUROCAT criteria (Broe et al., 2020). Major congenital anomalies were defined by excluding minor congenital anomalies based on the EUROCATS classification (see Supplementary S2).

2.7. Statistical analysis

Characteristics of the study population were tabulated in a contingency table for the exposed and unexposed cohort according to disease activity. We computed crude and adjusted relative risk estimates (prevalence odds ratio [OR] with corresponding 95 % confidence intervals [95 % CI]) for adverse neonatal outcomes following MS disease activity during pregnancy relative to no MS disease activity during pregnancy. In the regression model, we adjusted for maternal age at childbirth, parity, CCI, smoking, and calendar period. Major congenital anomalies were also adjusted for the use of DMT. DMT was only considered as a confounder for the outcome of congenital anomalies, since it had no impact on other outcomes.

The model took the clustering of children born by the same mother into account. All calculations were performed using Stata Release 17.0 (StataCorp).

2.8. Sensitivity /sub-analyses

We made sensitivity analyses with a restricted time period to examine the confounding impact of maternal BMI (since these data were available only from 2005 (Bliddal et al., 2018)).

3. Results

3.1. Description of the study population

During the 20-year study period, 2492 singleton children of women with MS were born alive. Table 1 presents the study characteristics of the exposed and unexposed cohort, including characteristics of the mother and the childbirth. A total of 273 children were born after exposure to maternal disease activity and 2219 children were born to women without disease activity during pregnancy.

The women with disease activity during pregnancy had a median age of 31 (inter-quartile range (IQR) 28–34) years at childbirth. They had a median disease length of 3.2 (IQR 1.0–6.6) years and 55 % gave birth to their first child. An almost identical proportion of women in the exposed and unexposed cohorts were smokers at conception (15 % vs. 14.5 %). The vast majority (81.3 %) had no comorbidities before pregnancy and 18.7 % had some comorbidity. In the unexposed group, 13.3 % had some comorbidity. There were 30.8 % with DMT use before or during pregnancy among women with disease activity, and most of these patients were treated with beta-interferons (data not shown). There were 4.4 % in the exposed cohort with preeclampsia and 30.8 % gave birth by caesarian section. In the unexposed cohort, 2.4 % had preeclampsia and 26.8 % gave birth by caesarian section. There was an almost identical proportion of children born by women with gestational diabetes in the two groups (1.8 % vs. 2.3 %).

3.2. Risk of adverse neonatal outcomes

Table 2 presents the outcomes; preterm birth, small for gestational age, low 5-minute Apgar score, and major congenital anomalies for children of women with disease activity during pregnancy, relative to children of women with no disease activity during pregnancy. The adjusted ORs of preterm birth, small for gestational age, and low 5-minute Apgar score were 0.92 (95 % CI 0.53–1.60), 1.19 (95 % CI 0.62–2.26) and 2.57 (95 % CI 0.93–7.15) respectively. The adjusted odds ratio of major congenital anomalies was 0.93 (95 % CI 0.48–1.83).

3.3. Sensitivity analysis

In the sensitivity analyses, we additionally adjusted for BMI, and we did not find altered estimates that changed our conclusions on neonatal outcomes (data not shown). Therefore, it was omitted from the model.

4. Discussion

This study reports important neonatal outcomes in a nationwide cohort of all children of women with MS in Denmark from 1998 to 2018 according to maternal disease activity during pregnancy. The results represent important information for pregnant women with MS and clinicians involved in counseling these women. We did not find any statistically significantly increased risk of adverse neonatal outcomes associated with in utero exposure to disease activity. Of clinically relevant findings, children exposed to maternal disease activity had an increased risk of preterm birth, small for gestational age, and low 5-

Table 1
Descriptive characteristics of the study population.

	Children born of women with multiple sclerosis having disease activity during pregnancy (exposed cohort) *N* = 273	Children born of women with multiple sclerosis without disease activity during pregnancy (unexposed cohort) *N* = 2219
Maternal age at childbirth, median (IQR), years	31 (28–34)	32 (29–35)
Maternal BMI, N (%)		
<18.5 (underweight)	10 (3.7)	87 (3.9)
18.5–24.9 (normal weight)	141 (51.7)	1043 (47.0)
25–29.9 (pre-obesity)	60 (22.0)	377 (17.0)
>30 (obesity)	23 (8.4)	186 (8.4)
Missing	39 (14.3)	526 (23.7)
Parity		
First child	149 (55.0)	989 (45.5)
Second or more	122 (45.0)	1186 (54.5)
Maternal comorbidity N (%)		
No comorbidity	222 (81.3)	1924 (86.7)
Some comorbidity	51 (18.7)	295 (13.3)
Cigarette smoking N (%)		
No	223 (81.7)	1817 (81.8)
Yes	41(15.0)	321(14.5)
Missing	9 (3.3)	81 (3.7)
Preeclampsia, N (%)	12 (4.4)	53 (2.4)
Gestational diabetes, N (%)	5 (1.8)	52 (2.3)
Mode of delivery, N (%)		
Vaginal birth	183 (67.0)	1605 (73.2)
C-section birth	90 (30.8)	588 (26.8)
Disease-modifying treatment (120 days prior to conception or during pregnancy) N (%)	84 (30.8)	451 (20.3)
Disease duration, years Median (IQR)	3.2 (1.0–6.6)	5.0 (2.6–8.3)
Calendar year of childbirth, N (%)		
1998–2003	35 (12.8)	442 (19.9)
2004–2008	51 (18.7)	548 (24.7)
2009–2013	102 (37.3)	599 (27.0)
2014–2018	85 (31.1)	630 (28.4)
Child's sex, N (%)		
Female	153 (56.0)	1083 (48.8)
Male	120 (44.0)	1136 (51.2)
Small for gestational age, N (%)	12 (4.4)	85 (3.8)
Preterm birth (<37 weeks), N (%)	28 (8.5)	124 (5.8)
Low 5-minute **Apgar score, N (%)**	7 (2.2)	13 (0.6)
Congenital anomalies (major) N (%)	11 (4.0)	90 (4.1)

minute Apgar score but none of the estimates reached statistical significance.

One recent nationwide study from Fink et al. (2023) found that 7.2 % of a Swedish cohort of women with MS experienced disease activity during pregnancy, and this subgroup of women had an almost 2.5 fold increased risk of a "medically indicated" preterm birth, which is supporting our finding of disease activity may be associated to preterm birth.

Former studies of pregnancy and birth outcomes among women with MS (not taking disease activity into account) indicate that women with MS have an increased risk of small for gestational age (Andersen et al., 2021; Chen et al., 2009; Dahl et al., 2005; Fink et al., 2023). Regarding preterm birth, the results of previous studies have been divergent. Three studies comparing women with MS to women without MS have found a significantly increased risk of preterm birth (Chen et al., 2009; Fink et al., 2023; MacDonald et al., 2019) among women with MS and four studies with a slightly, but not statistically significant, increased risk of preterm birth have been identified (Andersen et al., 2021; Dahl et al., 2008; Fong et al., 2018; Weber-Schoendorfer and Schaefer, 2009). Low Apgar score has only been reported to a limited extent and the results have been conflicting (Andersen et al., 2021; Goldacre et al., 2017; Mueller et al., 2002). No studies have found statistically significant increased risk on low Apgar scores when comparing women with MS and the background population of women. We found a higher proportion of children (2.6 %) born with a low 5-minute Apgar score in the exposed group, but based on only 7 cases. This proportion is though close to the proportion of 2.1 % with low 5-minute Apgar score found in the Swedish birth cohort of women with MS (Fink et al., 2023). The corresponding proportion was 0.6 % in the unexposed cohort. The proportion in the unexposed group is similar to comparable cohorts and the background population (Andersen et al., 2021; Bliddal et al., 2018; Jolving et al., 2023).

To our knowledge, no previous study has examined maternal disease activity during pregnancy in women with MS and the impact on neonatal outcomes. From a patient perspective, MS disease activity is associated with disruption of everyday life, continuity, and future plans and an overall concern of whether the symptoms will remit and whether the functional level can be regained. For pregnant women with MS going through a complicated pregnancy with an active disease, there will also be concerns about which consequences the course will have on their unborn child (Kosmala-Anderson and Wallace, 2013). Advancing the current knowledge with the results of this present study, it seems to be, that disease activity during pregnancy not constitute a significant further risk of the adverse fetal outcomes preterm birth and small for gestational age, than what is already known.

We have not found any association between disease activity during pregnancy and major congenital anomalies. The proportion was similar to the interval of 3.9–5.3 % that is in the background population, previously described by Broe et al. (2020) with data from the Danish Medical Birth Register in the same period 1997–2017.

This study is strengthened by a nationwide population of 2492

Table 2
Neonatal outcomes of mothers with multiple sclerosis and +/- disease activity during pregnancy.

	Exposed cohort/Children born of women with multiple sclerosis and disease activity, N (%) *N* = 328	Unexposed cohort/Children born of women with multiple sclerosis without disease activity, N (%) *N* = 2164	Crude odds ratio (95 % CI)	Adjusted odds ratio[a] (95 % CI)
Preterm birth	19 (7.0)	133 (6.0)	1.09 (0.66–1.81)	0.92 (0.53–1.60)
Small for gestational age	12 (4.4)	85 (3.8)	1.19 (0.64–2.21)	1.19 (0.62–2.26)
Low 5-minute Apgar score	7 (2.6)	13 (0.6)	4.44 (1.74–11.16)	2.57 (0.93–7.15)
Congenital anomalies[b]	11 (4.0)	90 (4.1)	0.91 (0.47–1.87)	0.93 (0.48–1.83)

[a] Adjusted for: maternal age at childbirth, maternal smoking, parity, comorbidity, and calendar year of birth.
[b] Additionally adjusted for: disease-modifying treatment prior to conception.

children born to women with MS during a study period of 20 years. The nationwide design provides an unselected cohort of women with MS and their offspring, and with the Danish universal healthcare and long-lasting routines of registrations in the healthcare system, we were able to use a complete study cohort (Schmidt et al., 2019). Furthermore, we collected our outcomes independently from the research question and exposure status reducing the risk of differential misclassification on the outcome. We have valid outcome measurements from the Danish Medical Birth Register and adjusted for important confounders. We believe that we have taken the most important confounders into consideration, but in an observational study like this, we can never rule out unmeasured and unknown confounding.

We identified women with MS having disease activity during pregnancy by using proxies and the arguments for choosing these were: (1) prescription of systemic corticosteroids 30 days prior to conception or during pregnancy, since systemic corticosteroid is the most established and validated treatment (Berkovich, 2013) for MS relapses, and by using redeemed prescriptions we will catch patients with milder disease activity treated in out-patient clinics. (2) hospitalization with MS as a primary diagnosis from conception to birth, by which we will catch patients with disease activity related to MS. (3) MRI scan of the brain performed during pregnancy, since the safety of MRI of pregnant women has not yet been definitively clarified (Ray et al., 2016) and according to the precautionary principle pregnant women are not MRI scanned if the examination can be postponed until after the birth. Therefore, we can assume that an MRI of the brain performed during pregnancy is on a compelling indication such as newly occurring neurological symptoms or a change in existing symptoms.

This study also has limitations. First of all, the registries do not contain information on MS disease activity, so we had to use proxies. We found a prevalence of 11 % of the study population of women with MS having disease activity during pregnancy, which is comparable to a German study from Langer-Gould et al. (2020) who have described, in an observational cohort study of pregnancy-related relapses from 2020 that a total number of 35 out of 461 (8 %) pregnant women with MS had disease activity during their pregnancy. The low prevalence of disease activity in our study population coinciding with a low prevalence of neonatal outcomes resulted in low statistical precision. However, this study builds on a nationwide study population of all live-born children of women with MS in Denmark over 20-years providing us with the largest possible cohort so far. A potential misclassification of disease activity, cannot be ruled out. The women with milder relapses, who do not have a corticosteroid prescription or hospital contact during pregnancy, will not be included in the exposed cohort but instead in the unexposed cohort causing a possible underestimation of the relative risks. However, this issue will apply equally in the exposed and unexposed groups, hence the potential misclassification will be non-differential and not influence our risk estimates.

5. Conclusion

In this nationwide cohort study of children born to mothers with MS from 1998 to 2018, we did not find any statistically significant association of disease activity during pregnancy and the neonatal outcomes of preterm birth, small for gestational age, low 5-minute Apgar score, and congenital anomalies. With these results, we suggest that disease activity of MS in pregnancy does not have a major impact on the neonatal outcomes. Replication in larger populations and different settings would still be needed.

Approvals and ethics

The study was approved by the Danish Data Protection Agency under the current joint notification of the Region of Southern Denmark (j.no. 20-12114). According to Danish law and legislation, ethical review board approval or patient consent is not required for register-based studies.

Consent for publication

Not applicable.

Availability of data and materials

Access to data from the national health registries requires approval from the Danish Data Protection Agency. All data are stored and analysed at a secure server at the Danish Health Authorities, where any interested researcher can apply for access to health data through an application to the Research Service at the Danish Health Data Authority (forskerservice@sundhedsdata.dk).

Author's information

Patient and relative representatives are part of the research council at the Center for Clinical Epidemiology, Odense University Hospital. Patients and relative representatives have been involved in the discussion of the ideas of the study and outcome assessments. Patient and relative representatives have not been part of the design of the study, data analyses, or the writing of the manuscript.

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CRediT authorship contribution statement

Mette Louise Andersen: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Line Riis Jølving:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Maria Iachina:** Supervision, Software, Methodology, Formal analysis, Writing – review & editing, Data curation. **Pavithra Laxsen Anru:** Supervision, Software, Methodology, Formal analysis, Data curation, Writing – review & editing, Conceptualization. **Egon Stenager:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Torben Knudsen:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Bente Mertz Nørgård:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105549.

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