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ORIGINAL PAPER

# Reproduction patterns among non-Hodgkin lymphoma survivors by subtype in Sweden, Denmark and Norway: A population-based matched cohort study

**Joshua P. Entrop**[1] | **Caroline E. Weibull**[1] | **Karin E. Smedby**[1,2] | **Lasse H. Jakobsen**[3,4] | **Andreas K. Øvlisen**[3] | **Ingrid Glimelius**[5] | **Anna Marklund**[6] | **Thomas S. Larsen**[7] | **Harald Holte**[8,9] | **Alexander Fosså**[8,9] | **Knut B. Smeland**[8] | **Tarec C. El-Galaly**[1,3,7] | **Sandra Eloranta**[1]

[1]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

[2]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden

[3]Department of Hematology, Clinical Cancer Research Center, Aalborg University Hospital, Aalborg, Denmark

[4]Department of Mathematical Science, Aalborg University, Aalborg, Denmark

[5]Department of Immunology, Genetics and Pathology, Cancer Precision Medicine, Uppsala University, Uppsala, Sweden

[6]Division of Gynecology and Reproduction, Department of Reproductive Medicine, Karolinska University Hospital, Stockholm, Sweden

[7]Department of Hematology, Odense University Hospital, Odense, Denmark

[8]Department of Oncology, Oslo University Hospital, Oslo, Norway

[9]K.G. Jebsen Centre for B Cell Malignancies, University of Oslo, Oslo, Norway

**Correspondence**
Joshua P. Entrop, Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, K2 Medicin, Solna, K2 Klinisk Epidemiologi, 171 77 Stockholm, Sweden.
Email: joshua.entrop@ki.se

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## Summary

Previous studies concerning reproductive patterns among non-Hodgkin lymphoma (NHL) survivors are scarce and those available have reported conflicting results. Treatment regimens vary considerably between aggressive and indolent NHL and studies of reproductive patterns by subtypes are warranted. In this matched cohort study, we identified all NHL patients aged 18–40 years and diagnosed between 2000 and 2018 from the Swedish and Danish lymphoma registers, and the clinical database at Oslo University Hospital ($n = 2090$). Population comparators were matched on sex, birth year and country ($n = 19\,427$). Hazard ratios (HRs) were estimated using Cox regression. Males and females diagnosed with aggressive lymphoma subtypes had lower childbirth rates ($HR_{female}$: 0.43, 95% CI: 0.31–0.59, $HR_{male}$: 0.61, 95% CI: 0.47–0.78) than comparators during the first 3 years after diagnosis. For indolent lymphomas, childbirth rates were not significantly different from comparators ($HR_{female}$: 0.71, 95% CI: 0.48–1.04, $HR_{male}$: 0.94, 95% CI: 0.70–1.27) during the same period. Childbirth rates reached those of comparators for all subtypes after 3 years but the cumulative incidence of childbirths was decreased throughout the 10-year follow-up for aggressive NHL. Children of NHL patients were more likely to be born following assisted reproductive technology than those of comparators, except for male indolent lymphoma patients. In conclusion, fertility counselling is particularly important for patients with aggressive NHL.

**KEYWORDS**
fertility, late effects of therapy, non-Hodgkin lymphoma

# INTRODUCTION

The number of long-term non-Hodgkin lymphoma (NHL) survivors is increasing worldwide. A recent study reported a 47% increase in the prevalence of NHL survivors in Sweden during the last 12 years, which is likely due to a combination of an increased NHL incidence and improved survival.[1]

NHL survivors face a risk of various side effects from treatment, including secondary malignancies, cardiovascular diseases and decreased fertility.[2,3] Impaired fertility can occur as a consequence of both the lymphoma disease itself,[4–10] and its treatment.[4,6,8,11–13] Recent studies have reported decreased childbirth rates in both male and female survivors of NHL overall,[14–16] whereas another study limited to relapse-free survivors reported childbirth rates similar to the general population.[17] To date, reproduction has been studied more extensively in Hodgkin lymphoma (HL), due to its comparably high incidence among individuals in younger ages. Studies on HL survivors reported recently similar results as for NHL survivors with childbirth rates similar to the general population.[16–19] Nevertheless, the absolute number of young adults (aged 18–40 years) diagnosed with NHLs is similar to that of HL,[20] which warrants more research on fertility issues also in these patients.

NHL is a heterogeneous group of malignant lymphoproliferative disorders with regard to disease aetiology, risk factors and standards of care.[21,22] No population-based studies have yet investigated reproductive patterns across NHL subtypes, albeit substantial heterogeneity in fertility among survivors may occur in light of the significant differences in treatment strategies and prognosis among NHL subtypes. Uncovering these possible differences is important to provide more personalized fertility counselling and to determine individual needs for fertility preservation.

In this study, we utilize data from three Nordic countries to disentangle subtype-specific reproductive patterns using a causal inference framework to increase the understanding of the total effect of NHL subtypes on childbirth rates up to 10 years after diagnosis.

# METHODS

## Study population

For this population-based matched cohort study, we identified 2423 newly diagnosed NHL patients aged 18–40 years, including all individuals with a verified NHL diagnosis (ICD-O 3ed.: 9670–9719) in the Swedish Lymphoma Register (SLR), the Danish Lymphoma Register (LYFO), or the clinical lymphoma database at Oslo University Hospital (OUH) during the years 2000–2018 (SLR), 2000–2017 (LYFO) and 2000–2016 (OUH database). Both the SLR and LYFO have nationwide coverage, whereas the OUH database includes information on lymphoma patients diagnosed at OUH which is the main referral hospital for the health region southeast in Norway, covering 55% of Norway's population. We excluded NHL patients who died ($n = 92$) or had a recorded refractory disease or early relapse ($n = 65$) within 9 months after diagnosis, that is start of follow-up, those with a history of solid organ- or allogeneic stem cell transplantation ($n = 13$; Table S1) or HIV ($n = 43$; Table S2), and those with a childbirth within 9 months after diagnosis ($n = 0$) to exclude patients that were pregnant while potentially receiving (immuno)chemotherapy treatment. For each NHL patient, we sampled 10 comparators from the general population with replacement matched on sex, birth year and country in Denmark and Sweden, and 5 for those diagnosed in Norway. All comparators were required to be alive and free of NHL at the start of follow-up (9 months after lymphoma diagnosis). The cohort was linked to national population registers and medical birth registers based on each individual's unique identification number.

## NHL subtype

NHL subtypes were classified both according to major histological and clinical characteristics based on ICD-O codes. Histological subtypes were categorized as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), T-/NK-cell lymphoma and other B-cell lymphomas (Table S3). Subtypes were additionally categorized according to their clinical manifestation as indolent, aggressive or unspecified (Table S4).

## Definition of the outcome

Childbirths during follow-up were obtained from the Medical Birth Registers, which include information on all live- and stillbirths from gestational week 12 in Norway, week 28 in Denmark (week 22 from 2004 onwards) and week 28 in Sweden (week 22 from 2008 onwards).[23,24] For the main analyses, both time to first childbirth and subsequent childbirths were considered irrespective of whether the child was conceived after assisted reproductive technology (ART) or not.

## Covariates

Information on age at index date (18–25, 26–40 years), calendar year of index date (2000–2005, 2006–2010, 2011–2015, 2016–2018) and country were obtained for all NHL patients and comparators from the lymphoma and general population registers. We additionally obtained information on education, and history of autoimmune disease for Swedish and Danish NHL patients and comparators. Education was measured as the maximal reached educational level (<10 years, 10–13 years, >13 years) from the Danish Status Register and the Swedish Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA). History of autoimmune disease was obtained from the Swedish and Danish in- and outpatient registers (Table S5).

## Assisted reproductive technology

Information on the use of ART after diagnosis was obtained for all childbirths of NHL survivors and comparators by linking the Danish IVF and the Swedish Q-IVF registers to individuals in the study population using each individual's unique personal identity number.[25,26] Both registers include information on ART treatments received in private and public clinics nationwide since 1994 in Denmark and 2007 in Sweden.

## Follow-up time

Each individual was followed from 9 months after index date until the date of first childbirth, death or diagnosis of NHL among comparators, whichever came first. Individuals were administratively censored on the 31st of December 2019, 2018 and 2017 in Sweden, Denmark and Norway, respectively, or after 10 years post-diagnosis. In the recurrent event analysis, individuals were not removed from the risk set at the date of first childbirth.

## Statistical analysis

A directed acyclic graph (DAG) was assumed to a priori determine a plausible causal model for the association between NHL exposure and reproduction (Figure S2).[27,28] In this context, education, age at diagnosis, history of autoimmune diseases, calendar year of diagnosis (index year) and country of residence were identified as potential confounders. In a supplemental analysis using data from Sweden and Demark, we additionally adjusted for education and history of autoimmune diseases, since this information was not available in the Norwegian data. All analyses were stratified by clinical or histological NHL subtypes and included an interaction between sex and case/comparator indicator to allow for effect modification by sex.

Cox regression was used to estimate adjusted hazard ratios (HRs) that contrasted childbirth rates among patients in each of the NHL subtypes with comparators. Time since diagnosis was split into two time-bands (<3/≥3 years).[18] The cut-off of 3 years has been chosen to capture an initial period of anticipated low childbirth rates due to the time required to finish potential treatments, achieve a pregnancy and deliver a child. The models further included a three-way interaction between time-band, sex and case indicator to allow for non-proportional hazards. Flexible parametric survival models (FPMs), with 3 degrees of freedom (DFs) for the baseline hazard function and 2 DFs for the time-varying effects of NHL case/comparator status, sex and their interaction, were used to estimate time-varying HRs. The same regression models were used to predict cause-specific cumulative incidence functions (CIFs) of childbirth in the presence of death as a competing event for NHL patients and comparators across NHL subtypes, as well as absolute differences thereof (ΔCIF).[29,30]

FPMs following the approach described by Andersen–Gill were employed together with the method proposed by Cook, Gosh and Lin to estimate the average number of childbirths after NHL diagnosis, including all childbirths during follow-up, in the presence of death as competing event, and differences thereof contrasting NHL patients and comparators.[31–33]

In a supplemental analysis, Andersen–Gill Cox models for recurrent events were fitted to estimate the total effect of NHL subtype on first and subsequent childbirths comparing NHL patients to their comparators.[33,34] The main analysis was repeated with additional adjustments for education and history of autoimmune disease in the subset of NHL patients identified in the SLR and LYFO and their comparators to assess the impact of known residual confounders.

All individuals with missing information on NHL subtype ($n = 120$) and their comparators ($n = 623$) were excluded from all analyses. A complete cases analysis is assumed to yield valid effect estimates based on the assumed missingness DAG shown in Figure S3.[35]

Analyses were carried out using the statistical software package R.[36] The study has been approved by the Regional Ethical Review Board in Stockholm (No. 2014/1017-32), the Danish Data Protection Agency (No. 2018-88) and the Regional Committee for Medical Research Ethics South East Norway (No. 2018/2209).

# RESULTS

We included a total of 2090 NHL patients from Sweden ($n = 1135$), Denmark ($n = 680$) and Norway ($n = 275$), and 19 427 matched comparators (Table 1). Clinical and histological subtypes were equally distributed across countries, with DLBCL being the most common clinical subtype (48.7%), followed by FL (20.0%) and T-/NK-cell lymphomas (14.3%). The majority of patients were diagnosed with an aggressive lymphoma subtype (66.8%). During follow-up, 22.2% of the NHL patients and 26.1% of the comparators had at least one childbirth. There were overall no differences in crude childbirth rates among NHL survivors diagnosed with different clinical and histological subtypes except for T-/NK-cell lymphomas (Table S6).

## Histological subtypes

Overall, both women and men diagnosed with DLBCL had lower childbirth rates compared to their matched comparators, whereas childbirth rates for FL, T-/NK-cell lymphomas and other B-cell lymphomas were similar to those of their matched comparators (Table 2). Childbirth rates among NHL patients were particularly low compared to comparators during the first 3 years after diagnosis for both female and male DLBCL patients ($HR_{females}$: 0.43; 95% CI: 0.30 to 0.62; $HR_{males}$: 0.62; 95% CI: 0.46 to 0.84), and among those diagnosed with other B-cell lymphomas ($HR_{females}$: 0.54; 95%

**TABLE 1** Baseline characteristics of NHL patients with complete information ($n = 2090$) and their matched comparators ($n = 19\,427$).

| | Overall | | | | Sweden | | | | Norway | | | | Denmark | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | | Comparators | | Cases | | Comparators | | Cases | | Comparators | | Cases | | Comparators | |
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| Overall | 2090 | | 19 427 | | 1135 | | 11 308 | | 275 | | 1373 | | 680 | | 6746 | |
| Sex | | | | | | | | | | | | | | | | |
| Males | 1220 | (58.4) | 11 344 | (58.4) | 644 | (56.7) | 6409 | (56.7) | 159 | (57.8) | 794 | (57.8) | 417 | (61.3) | 4141 | (61.4) |
| Females | 870 | (41.6) | 8083 | (41.6) | 491 | (43.3) | 4899 | (43.3) | 116 | (42.2) | 579 | (42.2) | 263 | (38.7) | 2605 | (38.6) |
| Age at diagnosis, years | | | | | | | | | | | | | | | | |
| 18–25 | 376 | (18.0) | 3443 | (17.7) | 205 | (18.1) | 1995 | (17.6) | 42 | (15.3) | 210 | (15.3) | 129 | (19.0) | 1238 | (18.4) |
| 26–40 | 1714 | (82.0) | 15 984 | (82.3) | 930 | (81.9) | 9313 | (82.4) | 233 | (84.7) | 1163 | (84.7) | 551 | (81.0) | 5508 | (81.6) |
| Nulliparous | | | | | | | | | | | | | | | | |
| No | 1030 | (49.3) | 9707 | (50.0) | 523 | (46.1) | 5701 | (50.4) | 139 | (50.5) | 680 | (49.5) | 368 | (54.1) | 3326 | (49.3) |
| Yes | 1060 | (50.7) | 9720 | (50.0) | 612 | (53.9) | 5607 | (49.6) | 136 | (49.5) | 693 | (50.5) | 312 | (45.9) | 3420 | (50.7) |
| Year of diagnosis | | | | | | | | | | | | | | | | |
| 2000–2005 | 641 | (30.7) | 6025 | (31.0) | 327 | (28.8) | 3265 | (28.9) | 74 | (26.9) | 369 | (26.9) | 240 | (35.3) | 2391 | (35.4) |
| 2006–2010 | 565 | (27.0) | 5114 | (26.3) | 292 | (25.7) | 2912 | (25.8) | 101 | (36.7) | 504 | (36.7) | 172 | (25.3) | 1698 | (25.2) |
| 2011–2015 | 604 | (28.9) | 5586 | (28.8) | 328 | (28.9) | 3264 | (28.9) | 84 | (30.5) | 420 | (30.6) | 192 | (28.2) | 1902 | (28.2) |
| 2016–2019 | 280 | (13.4) | 2702 | (13.9) | 188 | (16.6) | 1867 | (16.5) | 16 | (5.8) | 80 | (5.8) | 76 | (11.2) | 755 | (11.2) |
| No. children born ≥ 9 months after HL diagnosis | | | | | | | | | | | | | | | | |
| 0 | 1626 | (77.8) | 14 294 | (73.6) | 866 | (76.3) | 8079 | (71.4) | 213 | (77.5) | 1029 | (74.9) | 547 | (80.4) | 5186 | (76.9) |
| 1 | 302 | (14.4) | 3338 | (17.2) | 172 | (15.2) | 2081 | (18.4) | 41 | (14.9) | 245 | (17.8) | 89 | (13.1) | 1012 | (15.0) |
| >1 | 162 | (7.8) | 1795 | (9.2) | 97 | (8.5) | 1148 | (10.2) | 21 | (7.6) | 99 | (7.2) | 44 | (6.5) | 548 | (8.1) |
| Morphological subtypes | | | | | | | | | | | | | | | | |
| DLBCL | 1017 | (48.7) | – | – | 545 | (48.0) | – | – | 129 | (46.9) | – | – | 343 | (50.4) | – | – |
| FL | 417 | (20.0) | – | – | 222 | (19.6) | – | – | 57 | (20.7) | – | – | 138 | (20.3) | – | – |
| T-/NK-cell lymphoma | 299 | (14.3) | – | – | 186 | (16.4) | – | – | 32 | (11.6) | – | – | 81 | (11.9) | – | – |
| Other B cell | 357 | (17.1) | – | – | 182 | (16.0) | – | – | 57 | (20.7) | – | – | 118 | (17.4) | – | – |
| Clinical subtypes | | | | | | | | | | | | | | | | |
| Aggressive | 1397 | (66.8) | – | – | 746 | (65.7) | – | – | 189 | (68.7) | – | – | 462 | (67.9) | – | – |
| Indolent | 693 | (33.2) | – | – | 389 | (34.3) | – | – | 86 | (31.3) | – | – | 218 | (32.1) | – | – |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

**TABLE 2** Rates of first childbirth and hazard ratios (HRs) comparing NHL patients to comparators by sex and NHL subtypes.

| | NHL cases | | | | Matched comparators | | | | RR-test | HRs (95% CI) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. (%) | | Reproduction rate (95% CI) | | No. (%) | | Reproduction rate (95% CI) | | *p*-value | 9 months to 3 years | | 3 years to 10 years | | *p*-value |
| *Females* | | | | | | | | | | | | | | |
| Clinical subtypes | | | | | | | | | | | | | | |
| Aggressive | 580 | (66.7) | 33.8 | (28.2 to 40.2) | 5407 | (66.9) | 45.2 | (43.0 to 47.5) | 0.001 | 0.43 | (0.31 to 0.59) | 1.06 | (0.85 to 1.32) | <0.000 |
| Indolent | 290 | (33.3) | 31.1 | (23.8 to 40.1) | 2676 | (33.1) | 37.5 | (34.7 to 40.5) | 0.184 | 0.71 | (0.48 to 1.04) | 0.95 | (0.66 to 1.37) | 0.277 |
| Morphological subtypes | | | | | | | | | | | | | | |
| DLBCL | 451 | (51.8) | 32.0 | (25.9 to 39.2) | 4186 | (51.8) | 44.6 | (42.1 to 47.2) | 0.001 | 0.43 | (0.30 to 0.62) | 1.01 | (0.78 to 1.30) | <0.000 |
| FL | 169 | (19.4) | 27.3 | (18.7 to 38.5) | 1567 | (19.4) | 32.3 | (29.0 to 35.9) | 0.411 | 0.78 | (0.47 to 1.29) | 0.91 | (0.55 to 1.53) | 0.664 |
| T-/NK-cell lymphoma[a] | 130 | (14.9) | 42.9 | (29.9 to 59.7) | 1225 | (15.2) | 48.4 | (43.7 to 53.5) | 0.556 | 0.52 | (0.28 to 0.96) | 1.26 | (0.82 to 1.93) | 0.020 |
| Other B cell | 120 | (13.8) | 34.2 | (22.3 to 50.1) | 1105 | (13.7) | 44.2 | (39.4 to 49.4) | 0.237 | 0.54 | (0.27 to 1.05) | 0.99 | (0.60 to 1.63) | 0.155 |
| *Males* | | | | | | | | | | | | | | |
| Clinical subtypes | | | | | | | | | | | | | | |
| Aggressive | 817 | (67.0) | 35.1 | (30.2 to 40.6) | 7552 | (66.6) | 42.0 | (40.1 to 43.8) | 0.021 | 0.61 | (0.47 to 0.78) | 1.05 | (0.86 to 1.26) | 0.001 |
| Indolent | 403 | (33.0) | 34.8 | (28.0 to 42.7) | 3792 | (33.4) | 35.9 | (33.6 to 38.4) | 0.819 | 0.94 | (0.70 to 1.27) | 0.99 | (0.72 to 1.36) | 0.820 |
| Morphological subtypes | | | | | | | | | | | | | | |
| DLBCL | 566 | (57.6) | 32.8 | (27.1 to 39.3) | 5287 | (57.6) | 41.2 | (39.0 to 43.4) | 0.017 | 0.62 | (0.46 to 0.84) | 0.97 | (0.76 to 1.23) | 0.025 |
| FL | 248 | (25.2) | 30.5 | (22.6 to 40.2) | 2301 | (25.1) | 33.9 | (31.0 to 37.0) | 0.525 | 0.94 | (0.64 to 1.39) | 0.86 | (0.56 to 1.33) | 0.767 |
| T-/NK-cell lymphoma[b] | 169 | (19.4) | 48.6 | (35.8 to 64.4) | 1592 | (19.7) | 47.0 | (42.8 to 51.5) | 0.873 | 0.82 | (0.50 to 1.32) | 1.23 | (0.84 to 1.79) | 0.193 |
| Other B cell | 237 | (27.2) | 36.3 | (27.5 to 47.0) | 2164 | (26.8) | 38.5 | (35.3 to 41.9) | 0.730 | 0.66 | (0.41 to 1.04) | 1.19 | (0.85 to 1.67) | 0.042 |

*Note*: HRs were estimated using a Cox regression model including an interaction by time-band to estimate HRs for two time-bands, that is 9 months to 3 years, and 3 to 10 years after diagnosis. Test of rate ratios (RRs) between NHL patients and comparators were conducted using Ulm's exact method. Reproduction rates are presented per 1000 person-years.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma.

[a]Most common T-/NK-cell lymphoma subtypes among females were ALK-positive anaplastic large-cell lymphoma (45.4%, ICD-O 3ed: 9714/3), ALK-negative anaplastic large-cell lymphoma (27.7%, ICD-O 3ed: 9702/3) and mycosis fungoides (10.8%, ICD-O 3ed: 9700/3).

[b]Most common T-/NK-cell lymphoma subtypes among males were ALK-positive anaplastic large-cell lymphoma (41.4%), ALK-negative anaplastic large-cell lymphoma (23.7%) and mycosis fungoides (16.6%).

CI: 0.27 to 1.05; $HR_{males}$: 0.66; 95% CI: 0.41 to 1.04). Females additionally had decreased childbirth rates in this time frame when diagnosed with T-/NK-cell lymphomas (HR: 0.52; 95% CI: 0.28 to 0.96). Childbirth rates were similar to those of comparators after 3 years post-diagnosis across sex and histological subtypes (Table 2).

There were significant differences in the CIFs by sex and histological NHL subtypes (Table 3, Figure 1, Table S7). Both females and males diagnosed with DLBCL had lower CIFs up to 10 years post-diagnosis when contrasted to their matched comparators ($\Delta CIF_{females}$: −0.07; 95% CI: −0.11 to −0.02; $\Delta CIF_{males}$: −0.05; 95% CI: −0.10 to −0.01). Male FL and T-/NK-cell lymphoma patients had CIFs similar to their comparators. However, female patients diagnosed with FL and T-/NK-cell lymphomas had lower CIFs up to 2 years (ΔCIF: −0.03; 95% CI: −0.06 to −0.01) and 5 years (ΔCIF: −0.08; 95% CI: −0.14 to −0.01) post-diagnosis, respectively. Similar patterns were observed in the analysis of the mean number of childbirths (Figure 2, Table S7).

Males and females diagnosed with DLBCL or T-/NK-cell lymphoma had higher proportions of children born after the use of ART compared to their matched comparators. Proportions among male patients with FL were similar to comparators (Table 4).

## Clinical NHL subtypes

Overall, both female and male NHL patients diagnosed with an aggressive lymphoma subtype had childbirth rates below their matched comparators, whereas rates for patients with indolent subtypes were similar to their comparators (Table 2). Childbirth rates were 67% (HR: 0.43; 95% CI: 0.31 to 0.59) and 39% (HR: 0.61; 95% CI: 0.47 to 0.78) lower for females and males diagnosed with aggressive NHL subtypes compared to comparators, respectively, in between 9 months and 3 years after index date. After 3 years post-diagnosis, childbirth rates among males and females diagnosed with an aggressive subtype were similar to comparators. Childbirth rates for male and female patients diagnosed with an indolent lymphoma were not significantly different from comparators throughout the study period (Table 2).

We observed differences in the CIF of childbirth between NHL patients and comparators by sex and clinical NHL subtype (Table 3, Figure S5, Table S7). Both male and female NHL patients with an aggressive subtype had lower CIFs up to 10 years post-diagnosis ($\Delta CIF_{females}$: −0.06; 95% CI: −0.11 to −0.02; $\Delta CIF_{males}$: −0.04; 95% CI: −0.08 to −0.00). Among patients with an indolent subtype, only females had a lower CIF when contrasted to their comparators up to 2 years post-diagnosis (ΔCIF: −0.04; 95% CI: −0.06 to −0.02). Estimates of the mean number of childbirths showed similar patterns (Figure S5). Partners of male patients and female patients with aggressive subtype had an estimated average of 0.44 (95% CI: 0.37 to 0.50) and 0.39 (95% CI: 0.33 to 0.46) childbirths at 10 years after index date, whereas the numbers among comparators were 0.48 (95% CI: 0.45 to 0.50) and 0.50 (95% CI: 0.48 to 0.53), respectively (Table S6).

Among those who had a childbirth during follow-up, the use of ART was more common in both males and females previously diagnosed with an aggressive NHL compared to general population comparators (Table 4).

**TABLE 3** Differences in cause-specific cumulative incidence (ΔCIF) of childbirth by sex and NHL subtype in the presence of death as competing event.

| | Difference in CIF of first childbirth after HL diagnosis with 95% CI comparing cases to matched comparators | | | | | |
|---|---|---|---|---|---|---|
| | At 2 years | | At 5 years | | At 10 years | |
| *Females* | | | | | | |
| Clinical subtypes | | | | | | |
| Aggressive subtypes | −0.07 | (−0.08 to −0.06) | −0.08 | (−0.11 to −0.05) | −0.06 | (−0.11 to −0.02) |
| Indolent subtypes | −0.04 | (−0.06 to −0.02) | −0.03 | (−0.07 to 0.02) | −0.04 | (−0.10 to 0.01) |
| Morphological subtypes | | | | | | |
| DLBCL | −0.07 | (−0.08 to −0.05) | −0.08 | (−0.11 to −0.04) | −0.07 | (−0.11 to −0.02) |
| FL | −0.03 | (−0.06 to −0.01) | −0.03 | (−0.09 to 0.03) | −0.03 | (−0.10 to 0.04) |
| T-/NK-cell lymphoma | −0.07 | (−0.10 to −0.05) | −0.08 | (−0.14 to −0.01) | −0.03 | (−0.12 to 0.07) |
| *Males* | | | | | | |
| Clinical subtypes | | | | | | |
| Aggressive subtypes | −0.05 | (−0.06 to −0.04) | −0.04 | (−0.07 to −0.02) | −0.04 | (−0.08 to 0.00) |
| Indolent subtypes | −0.01 | (−0.03 to 0.01) | 0.00 | (−0.04 to 0.04) | −0.01 | (−0.06 to 0.04) |
| Morphological subtypes | | | | | | |
| DLBCL | −0.05 | (−0.06 to −0.04) | −0.05 | (−0.08 to −0.02) | −0.05 | (−0.10 to −0.01) |
| FL | −0.01 | (−0.04 to 0.02) | −0.01 | (−0.06 to 0.04) | −0.03 | (−0.09 to 0.03) |
| T-/NK-cell lymphoma | −0.02 | (−0.05 to 0.01) | 0.01 | (−0.05 to 0.08) | −0.01 | (−0.10 to 0.08) |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma.

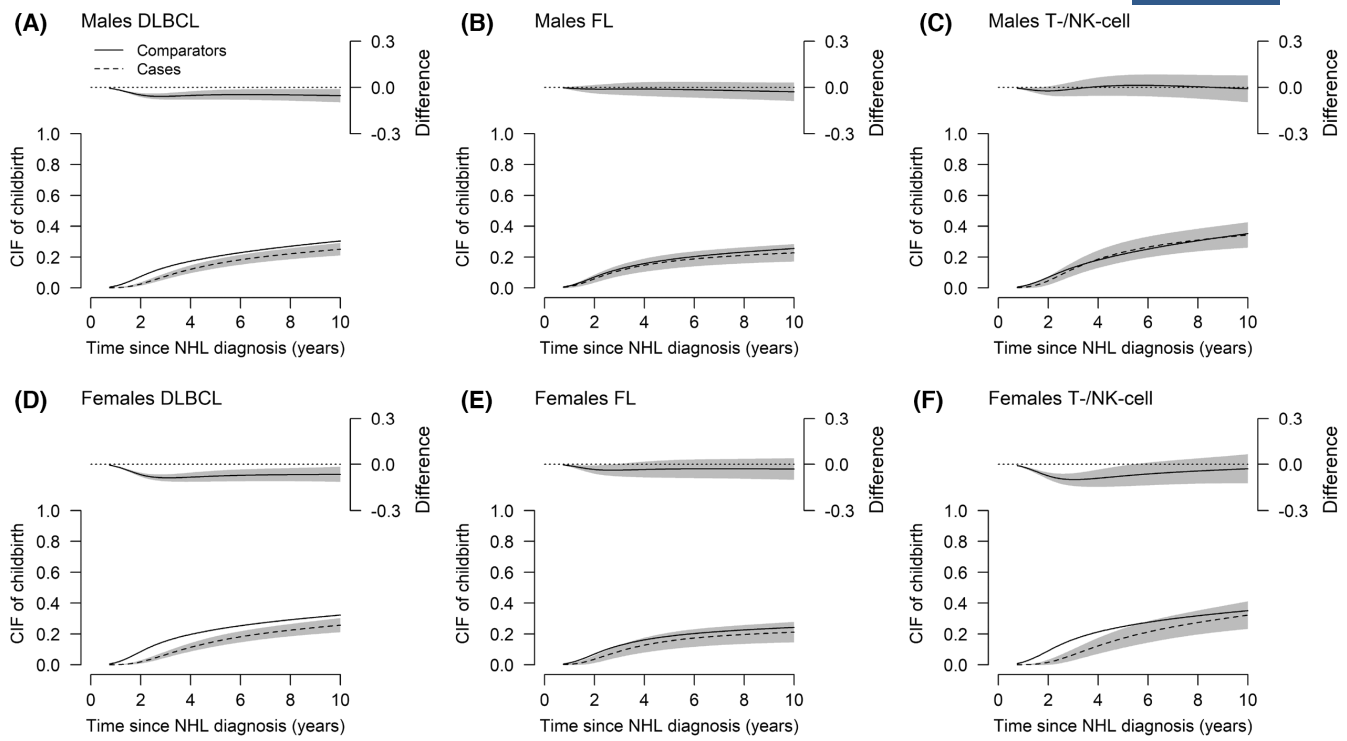


**FIGURE 1** Proportion of non-Hodgkin lymphoma (NHL) patients and comparators with a first childbirth after diagnosis by subtype for males (A–C) and females (D–F). Proportions across time since NHL diagnosis were estimated by the cause-specific cumulative incidence functions (CIF) in the presence of death as competing event. The upper part of the graph shows the difference in proportions between NHL cases and comparators.

Results for histological and clinical NHL subtypes were not altered when additionally excluding patients with a history of autoimmune disease ($n = 26$), or when additionally adjusting for education in the subset of NHL patients diagnosed in Denmark and Sweden (Tables S7, S9 and S10).

## DISCUSSION

In this Scandinavian population-based cohort study, we found that childbirth rates in NHL survivors were lower than among general population comparators for both male and female patients with an aggressive NHL subtype, specifically DLBCL, during the first 3 years post-diagnosis. Rates were additionally decreased for female T-/NK-cell lymphoma patients during the same period. However, after 3 years childbirth rates for both male and female patients were similar to their comparators among all clinical and histological subtypes. Nevertheless, the probability of having at least one child, as measured by the cumulative incidence, as well as the mean number of childbirths, was slightly lower throughout the entire follow-up for both male and female patients with DLBCL and other aggressive subtypes than in the matched population. The same pattern was observed for T-/NK-cell lymphomas, but only among females. Patients with an aggressive NHL subtype additionally conceived children more often with help of ART than their comparators.

Previous population-based studies have reported conflicting results concerning childbirth patterns among NHL overall while no studies have yet been able to differentiate between NHL subtypes. Two previous studies reported decreased childbirth rates among NHL patients compared to the general population.[14,15] These estimates are likely to be driven by the high prevalence of the DLBCL subtype among NHL patients in general.[1] Conversely, one study from Canada reported childbirth rates of NHL survivors similar to those of the general population.[17] However, survivors included in that study were required to be relapse-free until at least 5 years post-diagnosis which likely caused an underestimation of the difference for the whole population of NHL patients.

Decreased childbirth rates among NHL patients might be due to a combination of treatment toxicities, disease activity and changes in reproductive behaviour. These factors are likely to have a particularly strong impact on childbearing during the first years after diagnosis, whereas their impact might diminish with increasing time since diagnosis. Childbirth is closely related to fertility, which might be affected by toxic effects of NHL treatments on spermatogenesis[4,6,8] and ovarian function.[4,12,13] This is especially important for aggressive NHL subtypes which require immediate treatment often including high doses of alkylating agents and anthracyclines, whereas an initial wait-and-watch approach may be used for patients with indolent subtypes. However, using ART, pre-treatment fertility can sometimes be sufficiently restored through the use of cryopreservation of oocytes or sperm.[37] According to current international guidelines, timely information on infertility risks inherent

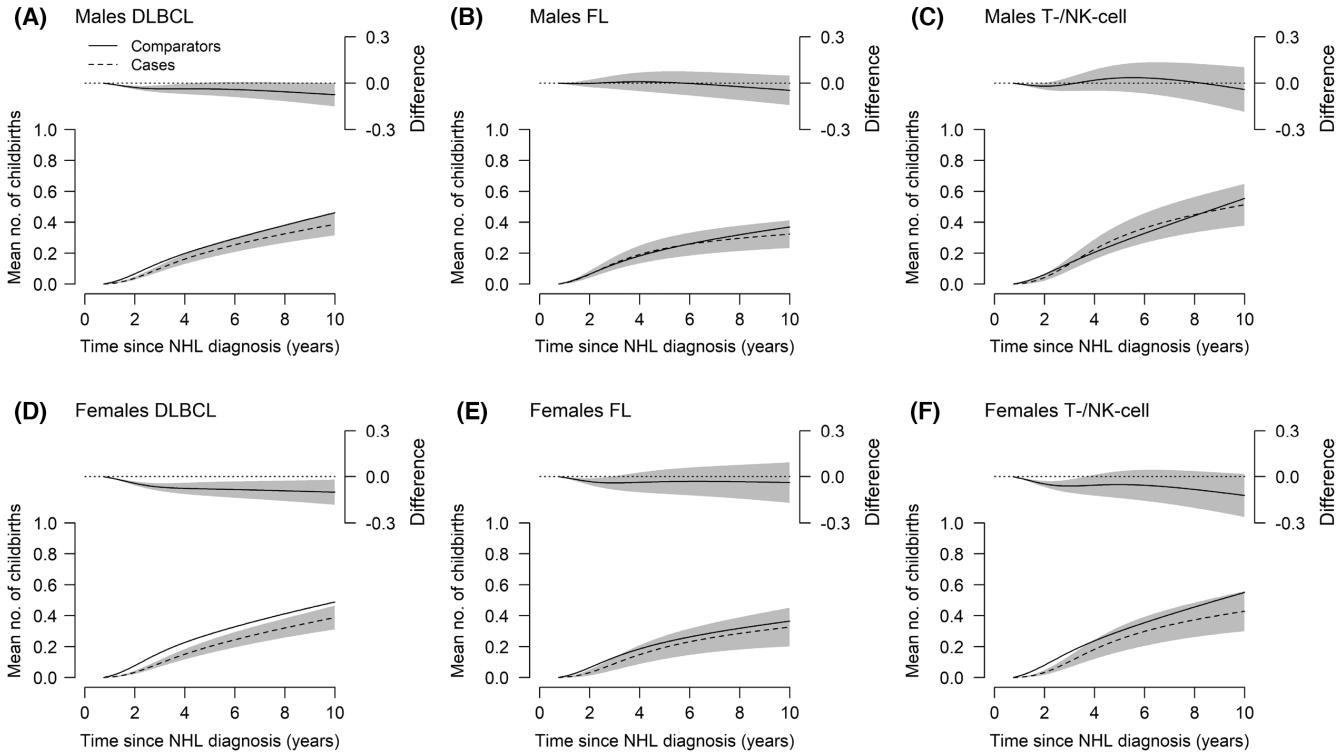


**FIGURE 2** Mean number of childbirths of non-Hodgkin lymphoma (NHL) patients and comparators by subtype for males (A–C) and females (D–F). The mean numbers were estimated taking death as competing event into account. The upper part of the graph shows the difference in mean numbers of childbirths between NHL cases and comparators.

**TABLE 4** ART treatment use among NHL survivors in Denmark and Sweden after 2007. The percentages (and 95% confidence intervals) represent the proportion of children who were conceived after ART treatment among all children born to the NHL survivors and comparators, respectively.

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases | | Controls | | Cases | | Controls | |
| | % | (95% CI) | % | (95% CI) | % | (95% CI) | % | (95% CI) |
| Clinical subtypes | | | | | | | | |
| Aggressive | 25.5 | (19.3–32.8) | 5.2 | (4.3–6.3) | 10.6 | (6.2–17.6) | 4.7 | (3.7–5.9) |
| Indolent | 10.8 | (5.8–19.3) | 5.6 | (4.2–7.3) | 5.9 | (2.0–15.9) | 6.2 | (4.5–8.4) |
| Histological subtypes | | | | | | | | |
| DLBCL | 23.1 | (16.2–31.9) | 5.4 | (4.3–6.7) | 10.7 | (5.7–19.1) | 4.9 | (3.8–6.4) |
| FL | 6.8 | (2.3–18.2) | 6.6 | (4.7–9.2) | <12.0 | –[a] | 4.2 | (2.5-7.0) |
| T-/NK-cell lymphoma | 27.3 | (16.3–41.8) | 4.1 | (2.6–6.4) | 12.9 | (5.1–28.9) | 4.2 | (2.6–6.7) |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma.

[a]Numbers cannot be disclosed due to low cell counts.

to gonadotoxic treatments should be provided to young adult cancer patients, with a referral to fertility counselling.[37] Additionally, fertility might be negatively affected by the disease itself. Some studies have reported decreased sperm counts and anti-Müllerian hormone concentration among NHL patients prior to treatment suggesting that spermatogenesis and ovarian reserve is also affected by disease activity.[4–10] Although these effects may be partly reversible by successful treatment, this may not always be the case. Finally, reproduction does not only depend on biological but also behavioural factors, for example, child wish and sexual activity, which might be affected by an NHL diagnosis and its treatment.[38–40]

National treatment guidelines for DLBCL and FL are relatively homogeneous across the Nordic countries. DLBCL patients are usually treated with R-CHOP, R-CHOEP or R-DA-EPOCH depending on risk factors and treatment areas. FL patients are commonly followed with a wait and watch approach and if needed treated with single rituximab, R-bendamustine or R-CHOP. GnHR agonists are not

commonly used across the Nordic countries and there exist no general guidelines in the Nordic countries recommending to refrain from childbearing after being diagnosed with or treated for NHL. However, some centres in the Nordic countries might still recommend against pregnancies for the first few years after NHL treatment.

Our study has several strengths. Firstly, the availability of population-based data from three Nordic countries provided us with sufficient power to analyse reproductive patterns among young males and females with the most common histological and clinical NHL subtypes. Secondly, the mandatory reporting to the registries,[24,41–43] the use of clinical databases with high coverage,[43] and the full access to specialized health care for all residents in the Nordic countries limit potential bias due to loss of follow-up or selection of included individuals.

Our study also faces limitations. We were not able to investigate childbirth rates among other distinct B-cell lymphoma subtypes such as mantle cell lymphoma, due to small numbers. We were not able to adjust for the potential confounding effect of education and history of autoimmune disease in our main analysis. Nevertheless, adjustment for these factors in the subset of patients diagnosed in Sweden and Denmark did not alter the direction of effects. Additionally, we were not able to estimate the direct effect of NHL subtypes on fertility. Instead, we estimated the total effect on reproduction, which includes possible mediators, for example, treatment and behavioural factors. Nevertheless, estimates of the total effect might be especially useful from a patient's perspective due to their relevance to real-world situations.[44] We were further only able to obtain data on the use of ART that resulted in a childbirth, but not on the overall use of ART among NHL patients and comparators.

In conclusion, we found that 10-year childbirth rates among NHL patients are similar to those of the general population. However, for both male and female DLBCL patients, the proportion of individuals with at least one childbirth and the average number of childbirths were slightly decreased up to 10 years after diagnosis. Thus, albeit having childbirth rates similar to the general population, DLBCL patients still do not catch up with regards to the proportion of individuals with first childbirths and the average number of childbirths up to 10 years post-diagnosis. Also, they more often require ART treatment to conceive. Our results convey a positive message for NHL survivors overall, but still underscore the importance of fertility counselling and fertility preservation in patients with DLBCL and other forms of aggressive lymphomas.

## AUTHOR CONTRIBUTIONS

All authors conceptualized the research project. Joshua P. Entrop, Karin E. Smedby, Lasse H. Jakobsen, Knut B. Smeland and Sandra Eloranta curated the data. Joshua P. Entrop and Sandra Eloranta performed the formal analysis. Joshua P. Entrop, Caroline E. Weibull, Lasse H. Jakobsen and Sandra Eloranta, developed and designed the methodology. Karin E. Smedby, Tarec C. El-Galaly and Sandra Eloranta acquiesced funding. Joshua P. Entrop, Karin E. Smedby, Tarec C. El-Galaly and Sandra Eloranta wrote the original draft. Sandra Eloranta supervised the project. All authors reviewed and edited the manuscript.

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## CONFLICT OF INTEREST STATEMENT

Joshua P. Entrop: None. Caroline E. Weibull: Red Door Analytics: Membership on an entity's Board of Directors or advisory committees; Janseen Pharmaceutical NV: Research Funding; War On Cancer: Ended employment in the past 24 months. Karin E. Smedby: Janseen Pharmaceutical NV: Research Funding. Lasse H. Jakobsen: Roche: Honoraria. Andreas K. Øvlisen: None. Ingrid Glimelius: Takeda: Research Funding; Janseen Cilag: Research Funding. Anna Marklund: None. Thomas S. Larsen: Genentech: Research Funding; Roche: Consultancy; Novartis: Consultancy; Gilead Sciences: Consultancy; Bristol Myers Squibb: Consultancy. Harald Holte: Nordic Nanovector: Honoraria, Other: Safety committee; Novartis: Honoraria, Other: Advisory board; Gilead: Honoraria, Other: Advisory board; Incyte: Honoraria, Other: Advisory board; Takeda: Honoraria, Other: Advisory board; Genmab: Honoraria, Other: Safety committee. Alexander Fosså: None. Knut B. Smeland: None. Tarec C. El-Galaly: Abbvie: Other: Teaching in 2021; Roche: Ended employment in the past 24 months. Sandra Eloranta: None.

## DATA AVAILABILITY STATEMENT

Individual-level data used for the analysis cannot be shared with others in accordance with EU's GDPR. A detailed analysis plan describing the data used for this study has been pre-registered online on the Open Science Framework together with the main statistical programs used for analysis (https://osf.io/a4u3d//).

## ETHIC STATEMENT

The study has been approved by the Regional Ethical Review Board in Stockholm (No. 2014/1017-32), the Danish Data Protection Agency (No. 2018-88) and the Regional Committee for Medical Research Ethics South East Norway (No. 2018/2209).

## ORCID

*Joshua P. Entrop* https://orcid.org/0000-0003-1614-8096
*Caroline E. Weibull* https://orcid.org/0000-0001-8231-8183

*Andreas K. Øvlisen* https://orcid.org/0000-0002-4631-9936
*Ingrid Glimelius* https://orcid.org/0000-0001-6158-3041
*Thomas S. Larsen* https://orcid.org/0000-0002-8418-6708
*Harald Holte* https://orcid.org/0000-0001-9799-9428
*Sandra Eloranta* https://orcid.org/0000-0001-5806-0573

## TWITTER

*Joshua P. Entrop* @entjos
*Caroline E. Weibull* @carolineweibull
*Karin E. Smedby* @ESmedby
*Ingrid Glimelius* @glimelius
*Knut B. Smeland* @KnutSmeland

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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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