Number of parity and the risk of non-Hodgkin lymphomas: a dose–response meta-analysis of observational studies

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ABSTRACT

Background: Epidemiological reports have shown that parity is associated with a risk of developing non-Hodgkin lymphomas (NHL). However, the findings have been inconsistent.

Methods: We searched the EMBASE and PubMed databases for eligible studies up to 10 March 2016. Category and generalized least square regression models were used to perform data analyses.

Results: In total, five cohort and seven case–control studies were identified. Categorical analyses indicated that parity number has little association with NHL and its subtypes. In dose–risk analyses, there were no relationships between parity and NHL risk (p for association = 0.064; n = 10). The summarized risk ratio (RR) was 0.97 (95% confidence interval (CI): 0.95–1.00; I² = 24.4%; P heterogeneity = 0.294; Power = 0.62) for each additional live birth. Similarly, for B-cell NHL, there was a null association between parity and NHL risk (p for association = 0.121; n = 5). The combined RR was 0.96 (95% CI = 0.90–1.03; I² = 63.7%; P heterogeneity = 0.026; Power = 0.71) for each additional live birth. For follicular NHL, there was still a non-significant association identified (p for association = 0.071; n = 4), the pooled RR was 1.00 (95% CI = 0.95–1.07; I² = 17.3%; P heterogeneity = 0.305; Power = 0.26) per additional live birth.

Conclusions: Our data identified little evidence suggesting that high parity is a protective factor against the development of NHL, including its B-cell and follicular subtypes.

Introduction

Non-Hodgkin lymphomas (NHL) are among the most common haematologic malignancies worldwide and have high-incidence rates in developed areas (the 10th highest in Europe and the UK) [1,2]. According to the most recent data from the International Agency for Research on Cancer (IARC), an estimated 385,700 new cases of NHL and 199,700 related deaths worldwide have occurred, corresponding to an incidence rate of 11.03 per 100,000 for men and 7.87 for women, with an upward trend [3].

In women, pregnancy involves dramatic alterations in oestrogen level, immune state and lifestyle, which may have a long-term influence on the prospective health of them [4–6]. Meanwhile, epidemiological studies [7] are increasingly focusing on whether reproductive factors among women may be related to a risk of developing NHL [5–8]. However, varying evidence has presented conflicting results. For example, in the California Teachers Study cohort, a 30% decreased risk of B-cell NHL associated with full-term pregnancies has been observed [8]. Similarly, a population-based cohort study in Taiwan has also found a protective role for each additional parity [9]. In contrast, though, data from the NIH-AARP Diet and Health Study Cohort have indicated null associations between NHL and parity in women [10]. In addition, an earlier systematic review [11] based on 7 studies has indicated a negative result. That review, however, did not include several relevant earlier studies [12–15], and the results were not based on a direct meta-analysis of the relationship between parity and NHL. Moreover, 2 additional large cohort studies have since been published [9,16].

Therefore, to further investigate the dose–risk relationships between parity and risk of NHL, we designed a systematic review and dose–response meta-analysis to summarize evidence from current individual studies.

Materials and methods

The meta-analysis methodology was designed following the Preferred Reporting Items for Systematic Reviews guidelines (PRISMA Checklists) for conducting meta-analyses of observational studies and reporting the results [17,18]. There were no ethical issues in...
obtaining the data derived from published articles for this meta-analysis [10].

**Publication search**

We performed a search of PubMed and EMBASE databases to identify relevant studies that contained information on the association between parity and NHL risk published up to 10 March 2016. The search was limited to studies carried out in humans, and the following key words and medical subject headings were used: (‘parity’ or ‘live birth’ or ‘pregnancy’ or ‘reproductive factor’ or ‘reproductive’ or ‘reproduction’) AND (‘non-Hodgkin lymphoma’ or ‘Hodgkin lymphoma’ or ‘Hodgkin’ or ‘lymphoma’ or ‘lymphoid neoplasms’ or ‘lymphadenoma’). In addition, we manually searched the reference lists of relevant articles, recent reviews and meta-analyses. No language restrictions were applied.

**Eligibility criteria**

The inclusion criteria for studies were: (1) cohort or case–control study design; (2) exposure of parity, and primary NHL as the outcome of interest; (3) reported risk ratio (RR) or odds ratio (OR) or hazard risk (HR) estimates and 95% confidence intervals (CI) for each category; and (4) at least three categories of parity number. Study selection was carried out independently by two reviewers (GP, HGC). Any disagreements were resolved by consensus or discussion with a third reviewer (ZQ).

**Data collection**

The following information was extracted from each study: author list, year of publication, study region, sample size (number of participants and cases), participants’ characteristics, range of follow-up studies, exposure ascertainment, multivariable-adjusted RR estimates with 95% CIs, and covariates adjusted in the variable analysis for data analysis. If multiple estimates were available, authors extracted the estimates that adjusted to the most covariates. Data extraction was conducted by one author (RL) and checked by a second reviewer (HGC). All disagreements were discussed and resolved by consensus.

**Quality assessment**

Quality assessment of observational studies was performed by using the Newcastle–Ottawa scale checklist [19]. Each included study was judged on the basis of three perspectives: the selection of study participants (four items), the comparability of studies based on the design or analysis (two items), and the evaluation of exposure in case–control studies or ascertained outcomes in cohort studies (three items). The checklist contained a total of nine items, and each item was awarded 1 point. A second reviewer (GP) also carefully checked the quality assessment.

**Statistical analysis**

We used Stata software (version 12.0; Stata Corp LP, TX, U.S.A.) to conduct statistical analyses. Two-sided tests were used, and p < 0.05 was regarded as statistically significant. For each study, RRs were applied to provide accurate estimates. Random-effects models were applied for data analysis [20].

Associations between the parity number and NHL risk were quantified by comparing the highest and lowest (the referent) categories. To use all of the exposure–disease information, including the intermediate categories, we performed a two-stage dose–response meta-analysis. For this procedure, we used the method described by Greenland [21,22] and Orsini [23,24]. Briefly, in the first stage, we modelled the parity number by using restricted cubic splines with a distribution of four knots at 5th, 35th, 65th, and 90th percentiles [25]. Next, three spline transformations were fitted in consideration of the correlation within each set of reported RRs [23]. In the second stage, we combined the 3 regression coefficients (4 knots minus 1) and variance matrices within each study by using multivariate extension method [16]. A p-value for the non-linear trend was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. When non-linearity was not detected, we performed generalized linear meta-regressions [21]. For each of the included studies, we assigned the reported median or mean parity number of each category as the category parity number. When the highest category was open ended, we calculated its category number as the lower bound plus 1.5 times the width of the closest category [26]. The statistical power of the results was evaluated by the method of Hedges and Cafri [27,28].

Heterogeneity was estimated by using the Cochran Q test [29] and the I² statistic [30], which represents the proportion of total variation attributable to true between-study heterogeneity. I² values of 25, 50, and 75% are often used to classify low, moderate, and high heterogeneity, respectively [23]. A p-value <0.05 indicated statistical significance. Stratified analyses and meta-regression were conducted in consideration of the substantial effect of potentially significant covariates on between-study differences [30–32]. Sensitivity analysis was used to test the robustness of the results by omitting one study at a time [31,33]. Egger’s test was used to evaluate publication bias [34–36].

**Results**

**Study identification and characteristics**

The literature search process is displayed in a flow diagram in Figure 1. Briefly, using our search strategy, we initially scanned 6346 records. Then, after omitting
duplicate articles, 4316 articles remained. Upon reviewing titles and abstracts, we identified 28 studies for further retrieval. To obtain the final set of eligible studies, we completely read the full text of the remaining articles, ultimately selecting 12 reports that met eligibility criteria. No new studies were added in the data search. In addition, one study [13] provided data separately for men and women, so we treated the datasets as independent studies. Therefore, we included 13 datasets in the meta-analysis.

A description of characteristics is given in Table 1. All 13 datasets were published between 1997 and 2015, and cumulatively, they involved a total of 8307 cases and 3,624,662 participants. Five studies were cohort designs [8–10,14,16,37] whereas seven were case–controls [12–15,38–40]. In the cohort studies, sample sizes ranged from 134,074 [10] to 2,024,770 [16], and the number of cases varied from 91 [10] to 1,546 [16]. In case–control studies, cases ranged from 177 [14] to 1,240 [12], and subjects varied from 234 [34] to 6,237 [31]. Seven studies were conducted in the U.S.A. [8,10,14–16,37,39], four in Europe [12,13,38,40], and one in Asia [9]. Most studies [5,6,7,27,34,35] adjusted for important confounding factors, such as age, race, study design, location, subject sources, smoking and alcohol consumption. All studies yielded an average score of 6.2 in the quality assessment, and there was a good concordance between reviewers (Kappa test = 0.793; see Table 2).

Parity number and NHL risk

Nine studies encompassing 10 datasets [9,10,12,13,15,16,37–39] reported an association between parity and NHL risk. We first applied categorical data analysis. Comparing the highest and lowest parities, the pooled RR was 0.89 (95% CI = 0.79–1.01, \( p_{\text{for association}} = 0.064 \)), and low heterogeneity was observed (\( I^2 = 24.9\% \); \( p_{\text{heterogeneity}} = 0.215 \); Figure 2).

In a dose–response analysis, little evidence supported a non-linear association between the groups (\( p \) for the non-linearity test was 0.311; Figure 3). Using the linear regression model, a null association between parity number and NHL risk was found (\( p_{\text{for association}} = 0.083 \)). The combined RR of NHL for a one-parity increment was 0.97 (95% CI: 0.95–1.00; Power = 0.79) with moderate heterogeneity (\( I^2 = 57.8\% \); \( p_{\text{heterogeneity}} = 0.014 \)).

Parity number and B-cell NHL risk

Five studies [8,10,14,38,40] investigated the association between parity and risk of B-cell NHL. In a categorical data analysis, the combined RR for the highest vs. lowest categories of the parity number was 0.83 (95% CI = 0.57–1.21, \( p_{\text{for association}} = 0.338 \)), and moderate heterogeneity was found (\( I^2 = 61.8\% \); \( p_{\text{heterogeneity}} = 0.033 \); Figure 4).

In a dose–response analysis, little evidence supported a non-linear association between the groups (\( p \) for the non-linearity test was 0.275; Figure 5). Using the linear regression model, a null association was identified between the groups (\( p_{\text{for association}} = 0.121 \)). The linear regression model suggested that, compared with nulliparous subjects, the combined RR for an increase in parity of one live birth was 0.96 (95% CI: 0.90–1.03; Power = 0.71), and there was moderate heterogeneity (\( I^2 = 63.7\% \); \( p_{\text{heterogeneity}} = 0.026 \)).

Parity number and follicular NHL risk

Four studies [8,10,15,38] investigated the relationship of parity to follicular NHL risk. For the category analysis, the pooled RR of the highest numbers of total parity compared with those for the lowest category was 1.07 (95% CI = 0.76–1.50, \( p_{\text{for association}} = 0.702 \)), and there was no statistically significant heterogeneity observed among the studies (\( I^2 = 2.5\% \); \( p_{\text{heterogeneity}} = 0.380 \); Figure 6).

In a dose–response analysis, little evidence supported a non-linear association between the groups (\( p \) for the non-linearity test was 0.257). The linear regression model suggested that the association of parity with follicular NHL risk was still not statistically significant (\( p_{\text{for association}} = 0.071 \); Figure 7). As compared with null parity, the pooled RR for follicular NHL risk was 1.00 (95% CI: 0.95–1.07; Power = 0.26) per additional live birth, with moderate heterogeneity (\( I^2 = 17.3\% \); \( p_{\text{heterogeneity}} = 0.305 \)).
| First author, publication year (reference), Country | Type | Study design | Cases and subjects/ (person-years) | Recruitment of time, age (year) | Number of parity | Effect estimates (95% CI) | Multi-adjusted factors | Multi-adjusted factors | NOS |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Lee et al., 2008 [15], U.S.A. | NHL | Case–Control (Population based) | 80/116 317/410 78/125 98/174 | 1988–1993, 21–74 | Nulliparae 1–3 | Reference | 1.10 (0.81–1.50) | Race, marital status, years of education, lifetime average number of alcoholic drinks, lifetime number of sexual partners, obesity. | 7 |
| Frisch et al., 2006 [16], U.S.A., female | NHL | Cohort (Hospital based) | 238/7010000 640/11530000 294/4480000 104/1450000 | 1968–1999, 15–44 | 1 | Reference | 1.10 (0.94–1.28) | Age, calendar period, marital status, age at birth of first child. | 8 |
| Frisch et al., 2006 [16], U.S.A., male | NHL | Cohort (Population based) | 361/6320000 769/9660000 305/3600000 | 1968–1999, 15–64 | 1 | Reference | 0.96 (0.64–1.09) | Age, calendar period, marital status, age at birth of first child, registered homosexual partnership status. | 8 |
| Adami et al., 1997 [12], Swedish | NHL | Case–Control (Population based) | 306/1450 557/2704 245/1421 90/457 | 1960–1990, 28–72 | 1 | Reference | 0.97 (0.82–1.14) | Age at diagnosis or enrolment and mutually for number of births and age at 1st birth. | 7 |
| Tavani et al., 1997 [13], Italy | NHL | Case–Control (Population based) | 30/107 96/203 54/138 42/205 | 1983–1992, 17–79 | 1 | Reference | 1.40 (0.80–2.30) | Age, study centre | 4 |
| Cerhan et al., 2002 [37], U.S.A. | NHL | Cohort (Population based) | 20/39706 | 1986–1998, 69.7 (mean) | Nulliparae 1–2 | Reference | 0.60 (0.33–1.10) | Marital status, farm residence, history of transfusion, diabetes, smoking, alcohol use, intake of red meat and fruit | 6 |
| Morton et al., 2009 [10], U.S.A. | NHL | Cohort (Population based) | 53/102225 2873352 114185814 212341640 | 1996–2002, 42–50 | Nulliparae 1 | Reference | 0.76 (0.48–1.20) | Age at baseline, race, education, menopausal status, use of oral contraceptives, calendar time | 7 |
| Mildon et al., 2010 [38], UK | NHL | Case–Control (Population based) | 50/56 219/226 120/112 | 1998–2003, 16–69 | Nulliparae 1–2 | Reference | 0.90 (0.60–1.40) | Age | 5 |
| Zhang et al., 2004 [39], U.S.A. | NHL | Case–Control (Population based) | 71/72 78/79 161/174 96/118 180/258 | 1996–2000, 21–84 | Nulliparae 1 | Reference | 1.10 (0.80–1.50) | Age, family history of non-Hodgkin's lymphoma, body mass index, menopausal status | 6 |
| Chen et al., 2015 [9], Taiwan | NHL | Cohort (Population based) | 174/15124112 170/15683361 | 1978–2009, 30–55 | 1 | Reference | 1.0 (0.60–1.60) | Age at recruitment, parity, marital status, years of schooling, birth place | 7 |
| Costas et al., 2012 [40], European | B–NHL | Case–Control (Population based) | 110/207 148/176 261/313 141/184 | 1998–2004, 60.6 (mean) | Nulliparae 1–3 | Reference | 0.77 (0.55–1.07) | Age, country, education | 5 |
| First author, publication year (reference), Country | Type | Study design | Cases and subjects/ (person-years) | Recruitment of time, age (year) | Number of parity | Effect estimates (95% CI) | Multi-adjusted factors | NOS |
|--------------------------------------------------|------|--------------|-----------------------------------|-----------------------------|----------------|--------------------------|-----------------------|-----|
| Nelson et al., 2001 [14], U.S.A. B–NHL           | Case–Control (Population based) | 24/28 17/23 42/35 36/29 58/62 43 112 | 1989–1992, 17–75 Nulliparae 1 2 3 ≥4 | Oral contraceptive use, level of education, place of birth | Reference 1.14 (0.64–2.95) 1.77 (0.76–4.13) 1.83 (0.77–4.33) 1.51 (0.63–3.64) | 6 |
| Mildon et al., 2010 [38], UK B–NHL               | Case–Control (Population based) | 26/56 82/226 | 1998–2003, 16–69 Nulliparae 1–2 ≥3 | Age at baseline | Reference 1.20 (0.70–2.10) 1.77 (0.76–4.13) 1.83 (0.77–4.33) 1.51 (0.63–3.64) | 5 |
| Morton et al., 2009 [10], U.S.A. B–NHL           | Cohort (Population based) | 10/105098 8/73285 29/185573 44/341171 | 1996–2002, 42–50 Nulliparae 1 2 ≥3 | Age at baseline, race, education, menopausal status, use of oral contraceptives, calendar time | Reference 1.10 (0.70–1.70) 1.14 (0.45–2.90) 1.61 (0.78–3.29) 1.18 (0.59–2.35) | 7 |
| Prescott et al., 2009 [8], U.S.A. B–NHL          | Cohort (Population based) | 29/266779 24/182735 37/351934 29/260357 32/242121 | 1995–1996, 33–92 Nulliparae 1 2 3 | Age at menarche, full-term pregnancies, age at first pregnancy, first full-term pregnancy | Reference 0.97 (0.52–1.83) 0.74 (0.43–1.29) 0.70 (0.40–1.23) 0.74 (0.43–1.26) | 6 |
| Lee et al., 2008 [15], U.S.A. FL                   | Case–Control (Population based) | 20/116 104/410 22/125 26/714 | 1988–1993, 21–74 Nulliparae 1–3 4 ≥4 | Race, marital status, years of education, lifetime average number of alcoholic drinks, lifetime number of sexual partners, obesity | Reference 1.40 (0.79–2.40) 0.89 (0.44–1.80) 0.77 (0.39–1.50) | 7 |
| Morton et al., 2009 [10], U.S.A. FL                | Cohort (Population based) | 13/105109 7/173280 31/185562 54/341185 50/56 219/226 120/112 | 1996–2002, 42–50 Nulliparae 1 2 ≥3 | Age at baseline, race, education, menopausal status, use of oral contraceptives, calendar time | Reference 0.77 (0.31–1.93) 1.35 (0.70–2.57) 1.28 (0.69–2.35) | 7 |
| Mildon et al., 2010 [38], UK FL                    | Case–Control (Population based) | 50/56 219/226 120/112 | 1998–2003, 16–69 Nulliparae 1–2 ≥3 | Age at menarche | Reference 1.10 (0.80–1.50) 0.90 (0.60–1.40) 0.90 (0.60–1.40) | 5 |
| Prescott et al., 2009 [8], U.S.A. FL               | Cohort (Population based) | 24/266779 17/182735 20/351934 24/260357 27/242121 | 1995–1996, 33–92 Nulliparae 1 2 3 ≥4 | Age at menarche, full-term pregnancies, age at first pregnancy, first full-term pregnancy | Reference 0.82 (0.40–1.68) 0.67 (0.36–1.25) 0.79 (0.43–1.46) 0.87 (0.49–1.56) | 6 |

NHL = non-Hodgkin lymphoma; B–NHL = B-cell NHL; FL = Follicular NHL; CI = Confidence interval; NOS = Newcastle–Ottawa scale.
| Study   | Year | Representativeness of exposed cohort | Representativeness of unexposed cohort | Ascertainment of exposure | Outcome was not present at start | Important Factor | Additional factor | Outcome | Exposure Follow-up long enough for outcomes to occur | Adequacy of follow-up | Total score |
|---------|------|-------------------------------------|----------------------------------------|----------------------------|---------------------------------|------------------|------------------|---------|-----------------------------------------------|----------------------|-------------|
| Frisch  | 2006 | 1                                   | 1                                      | 1                          | 1                               | 1                | 0                | 1       | 1                                             | 1                    | 8           |
| Cerhan  | 2002 | 1                                   | 0                                      | 1                          | 0                               | 0                | 0                | 1       | 1                                             | 1                    | 6           |
| Morton  | 2009 | 1                                   | 0                                      | 1                          | 1                               | 1                | 0                | 1       | 1                                             | 1                    | 7           |
| Prescott| 2009 | 1                                   | 0                                      | 1                          | 1                               | 1                | 0                | 1       | 1                                             | 1                    | 6           |
| Chen    | 2015 | 1                                   | 1                                      | 1                          | 0                               | 0                | 0                | 1       | 1                                             | 1                    | 7           |

A. Cohort studies (n = 5)

| Study   | Year | Definition of cases | Representativeness of cases | Selection of controls | Definition of controls | Important Factor | Additional factor | Exposure | Asscertainment | Same method for subjects | Non-response rate | Total score |
|---------|------|---------------------|-----------------------------|-----------------------|------------------------|------------------|------------------|----------|-----------------|------------------------|------------------|-------------|
| Lee     | 2008 | 1                   | 1                           | 1                     | 1                      | 0                | 1                | 0        | 1               | 1                      | 1                | 7           |
| Nelson  | 2001 | 1                   | 1                           | 1                     | 1                      | 0                | 0                | 1        | 1               | 1                      | 1                | 6           |
| Tavani  | 1997 | 0                   | 1                           | 0                     | 1                      | 1                | 0                | 0        | 1               | 0                      | 1                | 4           |
| Costas  | 2012 | 1                   | 1                           | 0                     | 1                      | 1                | 0                | 0        | 1               | 1                      | 0                | 5           |
| Adami   | 1997 | 1                   | 1                           | 1                     | 1                      | 1                | 1                | 1        | 1               | 1                      | 0                | 7           |
| Mildon  | 2010 | 1                   | 1                           | 0                     | 0                      | 1                | 1                | 0        | 1               | 1                      | 0                | 5           |
| Zhang   | 2004 | 1                   | 1                           | 1                     | 1                      | 1                | 0                | 0        | 1               | 1                      | 0                | 6           |

*If the exposure data was obtained from prescription database or medical record, a point was assigned.
*If adjusted for age, a point was assigned.
*If adjusted for alcohol drinks and obesity, a point was assigned.
*If follow-up period is ≥6 years, a point was assigned.
*If the completeness of follow-up was 70% or more, a point was assigned.
Stratified and meta-regression analyses

To explore the potential source of statistical heterogeneity among the studies and to assess the stability of the results, two methods were used. For NHL RRs, data were stratified according to study design, location, type of subjects-based, quality score, exposure confirmation, and adjusted covariates (smoking and alcohol use). Table 3 presents the results of stratified analyses per additional live birth and NHL risk association. There were no substantial changes in the pooled RRs in each stratified analysis, and thus the association among them was stable. Moreover, the interaction test via meta-regression revealed no significant associations between subgroups \( (p > 0.05) \). For B-cell and follicular NHL, we did not perform stratified analyses because of the

**Figure 2.** Forest plot of parity (highest vs. lowest) and NHL risk. Squares indicate study-specific RRs; horizontal lines indicate 95% CIs; diamond indicates the summary OR estimate with its 95% CI. CI: confidence interval; RR: risk ratios.

**Figure 3.** Analysis of the linear dose–response relationship between parity and NHL (RR). The solid and long dashed lines represent the linear estimated RR and its 95% CI (per one live birth increment).

**Figure 4.** Forest plot of parity (highest vs. lowest) and B-cell NHL risk. Squares indicate study-specific RRs; horizontal lines indicate 95% CIs; diamond indicates the summary RR estimate with its 95% CI. CI: confidence interval; RR: risk ratios.
tendency of limited samples to produce false positive results.

**Sensitivity analyses**

To further confirm the robustness of our results, we conducted several sensitivity analyses to test the influence of individual studies on the overall results. For NHL diseases, we applied a linear regression model to fit the association, re-evaluating summarized RRs of the remaining studies and omitting one single study at a time. After this analysis, the trends in the relationship of parity with the risk of developing NHL and its subtypes did not materially change. In addition, the range of the estimated effect did not exceed 0.1% (0.965–0.979), for NHL, B-cell and follicular NHL, respectively. Table 4 presents the results of sensitivity analyses.

Moreover, for NHL, the re-analysed RR estimate for each additional parity was 0.98 (95% CI = 0.96–1.00; $I^2 = 32.4\%$; $p_{\text{heterogeneity}} = 0.193$) after omission of the case–control designed studies [12,13,15,38].

**Power analysis and publication bias**

Power calculations were performed post hoc after all of the studies had been collected, by using the methodology described by Cafri et al. For the outcomes of NHL, B-cell and follicular NHL, a power of 79, 71, and 26 was determined to detect an RR = 0.78, 0.96 and 1.00 per additional live birth compared with null parity, respectively. The Egger’s test was used to assess publication bias. For NHL, no publication bias was observed among studies for the highest vs. lowest categories ($p_{\text{for bias}} = 0.761$) and per additional live birth ($p_{\text{for bias}} = 0.802$). For B-cell and follicular NHL, no evidence of publication bias was found via Egger’s test (data not shown).

**Discussion**

The current meta-analysis evaluated the potential association between parity number and NHL diseases based on five cohort and seven case–control studies with a pooled total of 8307 cases. Linear regression dose–response modelling revealed little evidence of a protective effect of parity on the risk of developing NHL, B-cell NHL and follicular NHL.

In our meta-analysis, for NHL, the findings of the current study were in line with those of most previous studies on this topic. For example, the results were similar to those reported in a systematic review [11] of three cohort and four case–control studies, although the detailed data of the meta-analysis have not been provided. Another pooled analysis [41] involving seven case–control studies also supports our findings. Further, the subgroup and sensitivity analyses showed consistent results, further supporting...
the conclusions. Larger samples yielded stronger results, owing to higher statistical power ($p = 0.79$) [31]. Although moderate heterogeneity was observed ($I^2 = 57.8\%; p = 0.014$), the test for interaction was not significant among subgroups. For B-cell NHL, we observed a non-significant reduced risk of B-cell NHL associated with parity per additional live birth (RR = 0.96, 95% CI = 0.90–1.03), which is in line with previous data [5,7,30,32,33], involving two large cohorts [5,7]. Sensitivity analysis showed robustness of the results, and we had 71% statistical power to detect a RR = 0.96 per additional live birth. For follicular NHL, the results should be treated with caution, owing to the limited number of original studies [5,7,27,30] that were included ($N = 4$), although sensitivity analysis showed stable results. More well-designed cohort studies are needed to confirm these findings.

A possible partial explanation for the null effect of parity on NHL risk is the diversity of the included studies, which may have influenced the real association. In epidemiological studies, adjusting for differences is crucial to the robustness of results, to avoid exaggeration or underestimation of risk estimates [16]. In the present meta-analysis, most study designs did not adequately control for important confounders, such as alcohol drinking [42], obesity [43] and education [4], although no statistically significant differences were observed in the subgroup analyses. Only one study considered the factor of family history of non-Hodgkin’s lymphoma. Unmeasured socioeconomic factors and lifestyles may also have contributed to heterogeneity, thus potentially affecting the results. Therefore, these residual confounding effects may have influenced the association between parity and NHL risk [4,16]. However, subject sources and selection of controls were not all community based. The study designs varied across all of the reviewed studies. Other variables such as geographic location and data collection methods may additionally have affected the association to some extent, although the related subgroup analyses yielded consistent directionality [28].

Several biological mechanisms may account for a possible link between parity and NHLs. With increasing parity, females have longer time exposure to high levels of varying oestrogen throughout their lives [9].

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**Table 3. Overall result and subgroup analyses of per one live birth on NHL risk.**

|                      | No. of reports | RR  | 95% CI   | $p$ for association | $I^2$, (%) | $p$ for heterogeneity | $p$ for heterogeneity |
|----------------------|----------------|-----|----------|---------------------|------------|-----------------------|-----------------------|
| Overall studies      | 10             | 0.97 | 0.95–1.00| 0.083               | 57.8       | 0.014                 |                       |
| Type of design       |                |     |          |                     |            |                       |                       |
| Cohort               | 5              | 0.98 | 0.95–1.01| 0.264               | 32.4       | 0.193                 | 0.972                 |
| Case-control         | 5              | 0.95 | 0.91–1.00| 0.031               | 57.5       | 0.070                 |                       |
| Geographic location  |                |     |          |                     |            |                       |                       |
| U.S.A.               | 6              | 0.98 | 0.94–1.01| 0.122               | 61.3       | 0.017                 | 0.722                 |
| Europe               | 3              | 0.94 | 0.88–1.00| 0.182               | 0.00       | 0.766                 |                       |
| Type of subjects     |                |     |          |                     |            |                       |                       |
| Population           | 9              | 0.97 | 0.95–0.99| 0.024               | 52.2       | 0.033                 | 0.746                 |
| Hospital             | 1              | 0.98 | 0.87–1.10| 0.853               | 0.00       | 0.000                 |                       |
| Exposure confirmation|                |     |          |                     |            |                       |                       |
| Self-reported        | 5              | 0.96 | 0.92–1.02| 0.231               | 5.90       | 0.373                 | 0.282                 |
| Direct-measurement   | 5              | 0.97 | 0.95–1.00| 0.021               | 67.3       | 0.016                 |                       |
| Study quality        |                |     |          |                     |            |                       |                       |
| NOS ≥ 7              | 5              | 0.98 | 0.96–1.01| 0.063               | 37.6       | 0.155                 | 0.529                 |
| NOS < 7              | 5              | 0.95 | 0.91–0.99| 0.001               | 27.6       | 0.245                 |                       |
| Adjustment for education |     |     |          |                     |            |                       |                       |
| Yes                  | 2              | 0.99 | 0.91–1.08| 0.008               | 37.2       | 0.129                 | 0.739                 |
| No                   | 8              | 0.97 | 0.95–0.99| 0.057               | 76.1       | 0.040                 |                       |
| Adjustment for smoking|     |     |          |                     |            |                       |                       |
| Yes                  | 2              | 0.97 | 0.95–1.00| 0.068               | 0.00       | 0.506                 | 0.311                 |
| No                   | 8              | 0.96 | 0.92–1.01| 0.104               | 56.3       | 0.025                 |                       |
| Adjustment for obesity|     |     |          |                     |            |                       |                       |
| Yes                  | 3              | 0.96 | 0.93–0.98| 0.142               | 25.3       | 0.107                 | 0.871                 |
| No                   | 7              | 0.97 | 0.95–1.00| 0.010               | 40.8       | 0.020                 |                       |

CI = Confidence interval; RR = Risk ratio; NOS = Newcastle–Ottawa scale; RR = relative risk.

*a* $p$ value for association.

*b* $p$ value for heterogeneity within each subgroup.

$c$ $p$ value for heterogeneity between subgroups with meta-regression analysis.
Basic research has suggested that hormones can cyclically reverse cytokine profile expression; that is, the Th1 cytokine pattern is inhibited while Th2 is enhanced [5]. The cytokine imbalances may disrupt the differential expression of Th1 and Th2, because some cytokines play a key role in Th1 and Th2 expression [40]. Moreover, IL13 polymorphisms of the Th2 pathway have been found to increase the risk of lymphoma for AG/AA and CT/TT genotypes, OR = 2.6, 95% (CI 1.2–5.5) [44]. In addition, genetic variations causing a shift of the Th1/Th2 response may play a vital role in the pathogenesis of NHL [45]. Other studies, however, have suggested that oestrogen inhibits secretion of IL-6, which has been suggested to be a growth factor in lymphoma [6,46], and that excessive progesterone indirectly stimulates production of B-cell antibodies [47,48], which defend against intracellular pathogens and cancerous cells. Thus, there is a lack of biological explanations for the potential role of parity in NHL risk. We suspect that both harmful and protective factors play important roles in the course of NHL development, but the two counteracting mechanisms most probably cancel each other out. This effect may explain the apparent absence of an association.

Our meta-analysis has some strengths. First, we explored the dose-risk relationships by using different models, in contrast to all previous studies on this topic. Second, to the best of our knowledge, this is the first meta-analysis directly investigating the association between higher parity and NHL risk, and in particular, its two most common subtypes. Third, a comprehensive and detailed literature search along with the inclusion of more cohort studies made our results more reliable. Additionally, the dose-risk, sensitivity, stratified and power analyses yielded adequate findings, thus increasing the overall validity of our results.

Our study also has some limitations. First, a portion of the identified studies comprised case–control designs, and most of the information was based on self-reporting [33]. However, a recall bias could not be ruled out, although there was no general awareness of a potential relationship between parity and NHL diseases. Second, most of the studies [5,7,30,32] did not control for important confounding risk factors, such as virus, family history of NHL, and smoking [7]; our results should be accepted with a cautious understanding. Thus, more well-designed cohorts are needed to confirm our findings. Third, it has been reported that inconsistencies persist when parity is examined by NHL histologic subtypes [49]. However, only a limited number of published studies met the criteria for inclusion in this meta-analysis. The real relationship could not be adequately assessed because of an insufficient number of samples. Fourth, there were seven studies [5,7,27,31,32,34,35] from the U.S.A., four studies [28,29,30,33] from Europe, and only one study [6] from Asia. Most of the participants in the included studies were non-Asian, and thus the results of our meta-analysis may not be applicable to Asians [26,31]. The extrapolation of these data to Asian samples should be performed with caution. Finally, as in any meta-analysis, the possibility of publication bias is a concern. However, the results from this study did not provide evidence for such a bias.

**Conclusions**

In summary, this dose–response meta-analysis suggests that parity is not significantly associated with the risk of NHL, including B-cell and follicular NHL. More prospective well-controlled cohort studies are needed to fully elucidate these associations.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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**Table 4. Relative risk with 95% CI of number of parity at per one live birth in comparison with null parity by omitting each article in sensitivity analysis for NHL, B-cell NHL and follicular NHL.**

| Study for NHL | Per one live birth | RR | 95%CI | p* | p** |
|---------------|--------------------|----|-------|----|-----|
| Adami 1997 [12] | 0.97 | 0.96–0.99 | 0.068 | 0.384 |
| Tavani 1997 [13] | 0.97 | 0.96–1.00 | 0.114 | 0.400 |
| Cerhan 2002 [37] | 0.97 | 0.95–1.00 | 0.041 | 0.367 |
| Zhang 2004 [39] | 0.98 | 0.96–1.00 | 0.121 | 0.324 |
| Frisch 2006 female [16] | 0.97 | 0.95–0.98 | 0.198 | 0.216 |
| Frisch 2006 male [16] | 0.98 | 0.96–1.00 | 0.048 | 0.624 |
| Lee 2008 [15] | 0.98 | 0.96–0.99 | 0.096 | 0.235 |
| Morton 2009 [10] | 0.98 | 0.95–1.01 | 0.131 | 0.217 |
| Mildon 2010 [38] | 0.97 | 0.95–0.99 | 0.115 | 0.521 |
| Chen 2015 [9] | 0.98 | 0.96–1.00 | 0.043 | 0.165 |
| Case–Control [12,13,15,38,39] | 0.98 | 0.96–1.00 | 0.193 | 0.753 |

| Study for B-cell NHL | Per one live birth | RR | 95%CI | p* | p** |
|----------------------|--------------------|----|-------|----|-----|
| Nelson 2001 [14] | 0.95 | 0.88–1.02 | 0.011 | 0.095 |
| Costas 2012 [40] | 0.99 | 0.94–1.04 | 0.093 | 0.535 |
| Mildon 2010 [38] | 0.95 | 0.88–1.02 | 0.024 | 0.145 |
| Morton 2009 [10] | 0.96 | 0.89–1.04 | 0.039 | 0.103 |
| Prescott 2009 [8] | 0.97 | 0.89–1.06 | 0.003 | 0.054 |

| Study for follicular NHL | Per one live birth | RR | 95%CI | p* | p** |
|--------------------------|--------------------|----|-------|----|-----|
| Mildon 2010 [38] | 0.99 | 0.93–1.05 | 0.306 | 0.761 |
| Morton 2009 [10] | 0.99 | 0.92–1.07 | 0.203 | 0.820 |
| Lee 2008 [15] | 1.02 | 0.93–1.12 | 0.514 | 0.916 |
| Prescott 2009 [8] | 1.03 | 0.96–1.10 | 0.170 | 0.113 |

**Note:** NHL = non-Hodgkin lymphomas; RR = Relative risk; CI = Confidence interval.

*p values for heterogeneity test.

**p values for non-linear test.**
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