The association between birth order and childhood brain tumors: a systematic review and meta-analysis

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The incidence of childhood brain tumors (CBT) has increased worldwide, likely resulting from the improvements of early diagnostics. We conducted a systematic review and meta-analysis to clarify the association between birth order and CBT. We followed established guidelines to systematically search Ovid Medline, PubMed, and the Cochrane Library for English language studies, published before March 2018. Quality assessment was performed using the Newcastle–Ottawa Scale. Meta-analysis provided pooled risk estimates and their 95% confidence intervals (CIs) for birth order and CBT. We identified 16 case–control studies with a total sample of 32 439 cases and 166 144 controls and three prospective cohort studies (i.e. 4515 incident cases of CBTs among 5 281 558 participants). Compared with first birth order, the meta-odds ratio for second birth order in case–control studies was 1.04 (95% CI: 1.01–1.07), that for third birth order was 0.98 (95% CI: 0.90–1.06), and that for fourth order was 0.85 (95% CI: 0.78–0.92). The meta-hazard ratio for second or higher birth order compared with first birth order in cohort studies was 1.00 (95% CI: 0.96–1.05). We found no association between birth order and CBT in both case–control and cohort study designs; the small association observed for fourth birth order deserves further consideration. ***European Journal of Cancer Prevention*** **28: 551–561**

European Journal of Cancer Prevention 2019, **28:**551–561

Keywords: birth order, childhood brain tumors, meta-analysis

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Received 16 May 2018 **Accepted** 6 July 2018

Introduction

It is estimated that there will be 3560 new cases of childhood brain tumor (CBT) diagnosed in 2018 (Ostrom *et al.*, 2017). The incidence of CBTs in the USA is 5.54 per 100 000 population for a total 5-year count of 16 941 incident cases. The incidence is higher in males than in females (5.69/100 000 vs. 5.24/100 000 population) (Ostrom *et al.*, 2017). The incidence trend of CBT in the US experienced two periods: (a) increasing trend during the mid-1980s and (b) stabilizing trend from 1987 to 2009. During mid-1980s, there were significantly increased trends in incidence of pilocytic astrocytoma, primitive neuroectodermal tumor/medulloblastoma, and mixed glioma (McKean-Cowdin *et al.*, 2013). In addition, the incidence of CBTs has increased worldwide, likely resulting from the improvements of early diagnostics and changing in CBT classification (de Robles *et al.*, 2015). It is estimated that the incidence rate of all CBT worldwide is 10.82 [95% confidence interval (CI): 8.63–13.56] per 100 000 person-years (de Robles *et al.*, 2015).

Efforts have been made to evaluate the risk factors for CBTs. The only known and strong risk factors for CBT are the Li–Fraumeni syndrome and ionized radiation [reviewed by, Johnson *et al.* (2014)]. Although both genetic and environmental factors are suggested roles in CBT, birth characteristics, including birth order, maternal age, and mode of delivery, might present the interactions between genetic susceptibility and perinatal environmental causes (Johnson *et al.*, 2014).

Birth order has been hypothesized to play important roles in CBT carcinogenesis owing to its possible role as proxy for (a) reduced opportunity to early infection exposure and (b) hormone levels as first pregnancy differs endocrinologically from later pregnancies. Birth order is considered as a marker of different hormonal exposures to

Supplemental digital content is available for this article. Direct URL citationsappear in the printed text and are provided in the HTML and PDF versions of thisarticle on the journal's website, www.eurjcancerprev.com.

DOI: 10.1097/CEJ.0000000000000490

the fetus, and higher birth order children might have higher levels of microchimerism (Adams and Nelson, 2004). Additionally, birth order also has been used as a proxy for postnatal infectious exposures (Von Behren *et al.*, 2011).

The association between birth order and CBT has been examined; however, the results were inconclusive. Part of the reason for such inconclusiveness is the heterogeneity of the diseases and difference in methods used for and completeness of case ascertainment at different cancer registries (Johnson *et al.*, 2014). To our knowledge, no effort to date has been made to address the issue of inconsistency in the association between birth order and CBT. We, therefore, conducted a systematic review and meta-analysis to clarify the association between birth order and CBT.

Methods

Search strategy

Between June 2017 and March 2018, two investigators (M.V.N. and M.T.T.) conducted a systematic search to identify published studies up to March 2018. Owing to the rarity of disease, we did not limit the earlier date and year to optimize our search. Three databases (i.e. Ovid Medline, PubMed, and Cochrane Library) were searched using the following search terms: 'birth order' AND 'childhood brain cancer OR childhood brain tumors OR medulloblastoma OR PNET OR astrocytoma OR Low-grade astrocytoma OR High-grade astrocytoma OR ependymoma OR glioma OR juvenile pilocytic astrocytoma OR hypothalamic glioma OR oligodendroglioma OR hemispheric astrocytoma OR ganglioglioma OR brainstem glioma OR glial tumor OR CNS tumor or embryonal tumor'.

Study screening and selection criteria

We used published guidelines for reported observational studies (Strengthening the Reporting of Observational Studies in Epidemiology) (von Elm *et al.*, 2007) and systematic review and meta-analyses (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher *et al.*, 2009) for evaluating studies to be included in this meta-analysis. Inclusion criteria were English language report of original research in human subject that provided full estimates (i.e. odds ratios or hazard ratios or relative risks or risk ratios) and their respective 95% CIs. We further excluded articles if they were review papers or case-report papers or provided results from animal model studies. For example, in a study by McCredie *et al.* (1999), even though estimates were provided sufficiently, we could not use them, as the reference group (i.e. no birth) was different from the reference group we used in our current meta-analysis (i.e. first child); thus, we excluded this full-text article from our meta-analysis. All citations were independently reviewed by two investigators (M.V.N. and M.T.T.). Any discrepancies were resolved by discussion and consensus between the two investigators and in consultation with a senior author (H.N.L).

Data abstraction and coding

After the review process, two investigators (M.V.N. and M.T.T.) extracted data on the characteristics of the study. For each eligible study, information included in the table of characteristics was first author's name, year of publication, and country of study conducted; study design and sample size; sources of population (i.e. sources of cases and controls for case–control study or sources of incident cases for cohort studies); study period; age at diagnosis; covariates used to control for confounding factors in the multivariable models; and major results (i.e. estimates and their respective 95% CIs).

Quality assessment of selected studies

As the current systematic review and meta-analysis was performed in observational studies (i.e. case–control design or cohort design), we used the Newcastle–Ottawa scale for nonrandomized studies (Wells *et al.*, 2013) to assess quality of selected studies. In brief, the scale examined quality of case–control study based on (a) selection of study groups (i.e. selection of case and control groups); (b) comparability of cases and controls on the basis of the design or analysis; and (c) ascertainment of the exposure group. Similarly, the quality of a cohort study was assessed based on (a) selection of exposed cohort, (b) comparability of the cohort on the basis of the design or analysis, and (c) ascertainment of the outcome. A maximum score of 9 (or stars: selection of study group/exposed cohort = 4, comparability = 2, and ascertainment of exposure/outcome = 3) can be obtained for each study, meaning that higher score indicates a higher quality.

Statistical analysis

We calculated weight for log odds ratios for case–control studies and log relative risks for cohort studies by the inverse of their variance. These were used to calculate summary estimates (i.e. odds ratios or relative risks/hazard ratios) and their respective 95% CIs. DerSimonian and Laird random-effect model (DerSimonian and Laird, 1986), for both within-study and between-study variation, was used to combine studies in our meta-analysis. Q and I^2 statistics were used to evaluate statistical heterogeneity among studies. Specifically, P value less than 0.1 was considered statistically significant heterogeneity for Q statistics and I^2 was the proportion of total variation contributed in between-study variation (Higgins and Thompson, 2002). Publication bias was evaluated using funnel plots and Egger's regression asymmetry test in which P value less than 0.1 was considered statistically significant publication bias (Egger *et al.*, 1997). We also performed stratified analysis by geographical regions (i.e. USA and/or Canada, Europe, and others including

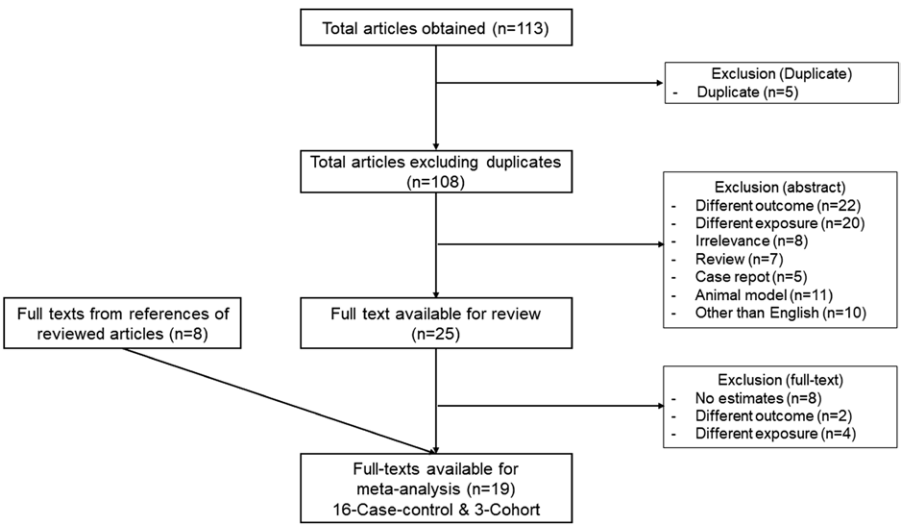
Australia and Brazil) and whether the reported results from models were adjusted for age at diagnosis. All statistical analyses were conducted using METAN command in Stata statistical software, version 15.0 (StataCorp., College Station, Texas, USA). All tests were two sided and were considered significant at the level of *P* value less than 0.05.

Results

We identified 16 case–control studies (Kuijten *et al.*, 1990; Emerson *et al.*, 1991; McCredie *et al.*, 1994; Savitz and Ananth, 1994; Linet *et al.*, 1996; Schüz *et al.*, 1999; Shaw *et al.*, 2006; Mallol-Mesnard *et al.*, 2008; Harding *et al.*, 2009; MacLean *et al.*, 2010; Schmidt *et al.*, 2010; Von Behren *et al.*, 2011; Oksuzyan *et al.*, 2013; Greenop *et al.*, 2014; de Paula Silva *et al.*, 2016; Vienneau *et al.*, 2016) and three prospective cohort studies (Heuch *et al.*, 1998; Mogren *et al.*, 2003; Schüz *et al.*, 2015) of birth orders and CBTs (Fig. 1). Of the case–control studies, six (Kuijten *et al.*, 1990; Emerson *et al.*, 1991; Shaw *et al.*, 2006; MacLean *et al.*, 2010; Von Behren *et al.*, 2011; Oksuzyan *et al.*, 2013) were conducted in the USA or Canada, seven (Savitz and Ananth, 1994; Linet *et al.*, 1996; Schüz *et al.*, 2001; Mallol-Mesnard *et al.*, 2008; Harding *et al.*, 2009; Schmidt *et al.*, 2010; Vienneau *et al.*, 2016) from Europe, two (McCredie *et al.*, 1994; Greenop *et al.*, 2014) from Australia, and one (de Paula Silva *et al.*, 2016) from Brazil. Among the three prospective cohort studies, one was from Norway (Heuch *et al.*, 1998), one from Sweden (Mogren *et al.*, 2003), and the other study from Denmark (Schüz *et al.*, 2015). The total sample size for 16 case–control studies was 32 439 cases and 166 144 controls, and among the three prospective cohort studies, 4515 incident cases of CBTs were included with a total follow-up of 5 281 558 study participants. Among 16 case–control studies, the study with the smallest sample size included 245 [in Australia (McCredie *et al.*, 1994)] and largest sample size included 75 638 in California, USA (Von Behren *et al.*, 2011). Most cases were identified from population cancer registries and/or birth registries, whereas controls were randomly selected and matched from population catchment. Moreover, most selected studies used the age at diagnosis definition of 0–14 years of age, except one study in Denmark (Vienneau *et al.*, 2016) using a cut-off of 7–19 years of age. Common covariates used in the multivariable models included sex, age at diagnosis, parents' level of education, and birth weight. The mean scores of the Newcastle–Ottawa scale were 3.74, 2.0, and 2.32 for selection of case/control group/exposed cohort, comparability, and ascertainment of exposure/outcome components, respectively (Supplemental Table 1, Supplemental digital content 1, *http://links.lww.com/EJCP/A221*); thus, total nonrandomized studies score was 8.06 (Table 1).

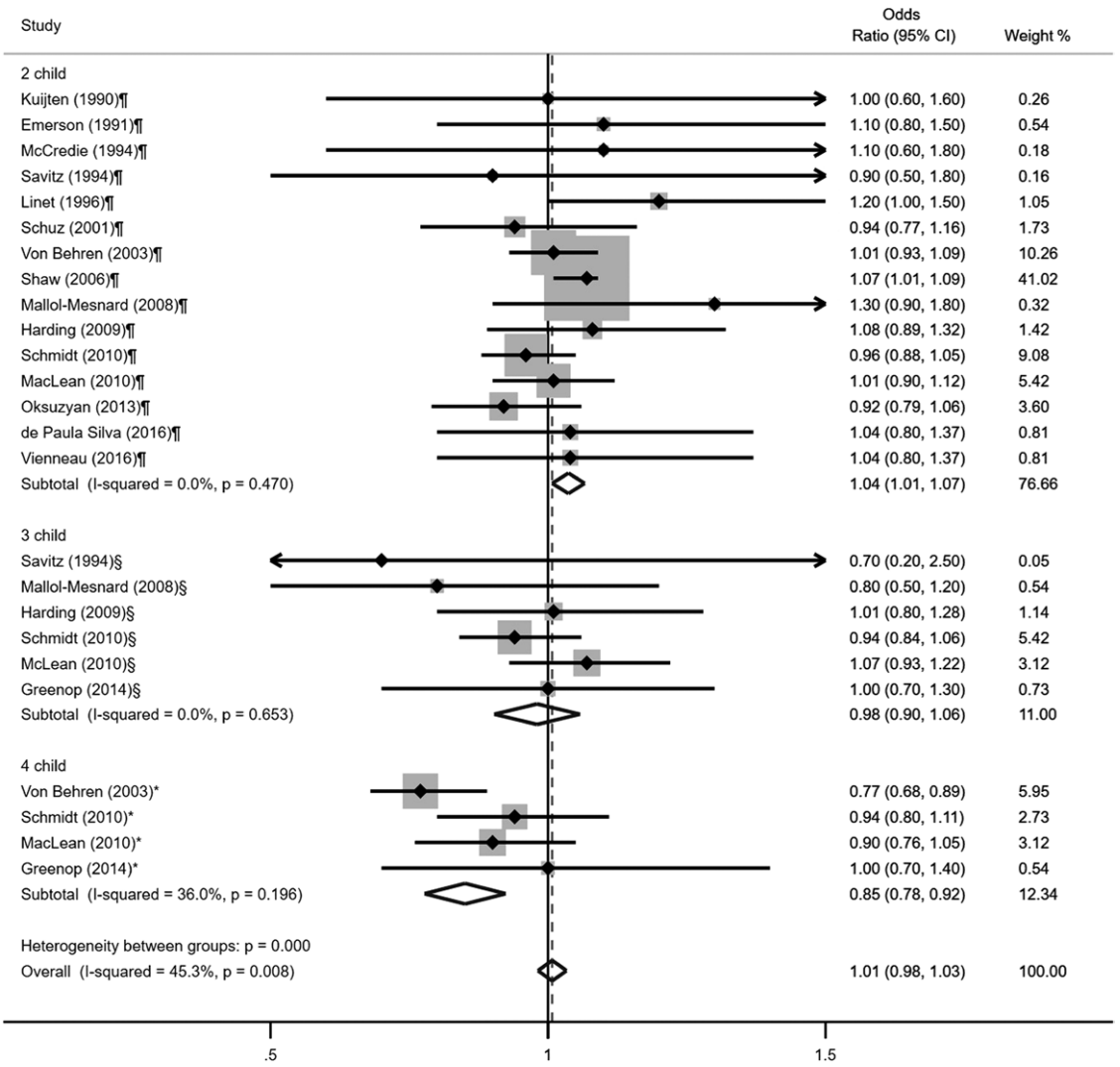
The association between birth order and CBTs is presented in Fig. 2. Compared with first birth order, the meta-odds ratio (mOR) for second birth order in case–control studies was 1.04 (95% CI: 1.01–1.07), that for third birth order was 0.98 (95% CI: 0.90–1.06), and that for fourth birth order or higher was 0.85 (95% CI: 0.75–0.92). The pooled-odds ratio of second or higher birth order, compared with first birth order, was 1.01 (95% CI: 0.98–1.03). The meta-hazard ratio for second or higher birth order compared with first birth order in cohort studies was 1.00 (95% CI: 0.96–1.05) (data not shown). Sufficient studies did not exist to perform stratified meta-analysis by histologic subtypes of CBTs.

Fig. 1



Flowchart for screening and eligibility evaluation process.

Fig. 2



Forest plot of the association between birth orders and childhood brain tumors in case–control studies. CI, confidence interval.

The funnel plot to evaluate the publication bias for 16 included case–control studies in this meta-analysis shows that there was no publication bias in our meta-analysis (Fig. 3). The heterogeneity tests show insignificant results. Accordingly, the Q heterogeneity test and its P value as well as I^2 for second birth order, third bird order, and fourth birth order were 13.73, 0.48, and 0.00; 4.69, 0.65, and 0.00; and 4.69, 0.20, and 36.00, respectively (data not shown). A sufficient sample size was not present to perform publication bias for prospective cohort studies in our current meta-analysis.

In stratified analysis (Table 2), we did not observe significant association between birth order and the risk of CBTs in studies across geographic regions. Accordingly, the mORs and their respective 95% CIs for second or higher birth order, in comparison with the first birth order, in the studies in the USA and Canada, Europe, and Australia and Brazil were 1.01 (0.97–1.03), 0.97 (0.92–1.03), and 1.02 (0.85–1.19), respectively. Moreover, in the stratified analysis, the mOR while age at diagnosis was included in the multivariable model of individual study was 0.94 (0.91–0.98) and 1.07 (1.03–1.11) while age was not included in the multivariable model (Table 2).

Discussion

In the current meta-analysis of 16 case–control studies and three prospective cohort studies, we found no overall association between birth order and childhood birth tumors in both case–control and cohort study designs; however, there was an inverse association in case–control studies for fourth birth order. Moreover, the studies that adjusted for age at diagnosis suggested a small but statistically significant inverse association.

Table 1 Characteristics of included studies in current meta-analysis

References, countries	Study design – sample size	Sources of population	Study period	Age at diagnosis	Covariates	Results (estimates and 95% CI)
Kuijten *et al.* (1990), USA	Case–control (163 cases vs. 163 controls)	Cases: tumor registries Controls: random digit, matched by age, race, and phone number	1980–1986	<15 years	Demographics	Astrocytomas: OR=1.0 (0.6–1.6) – first child vs. >1 child
Emerson *et al.* (1991), USA	Case–control (157 cases vs. 785 controls)	Cases: Cancer Surveillance System (population-based tumor registry) Controls: randomly selected from state birth file (5: 1), matched by birth year and county	1974–1986	<10 years	Age and county of residence	All: ≥second child as reference group OR=1.1 (0.8–1.5) Astrocytoma: OR=0.8 (0.4–1.3) Ependymoma: OR=1.3 (0.5–3.3) Medulloblastoma: OR=1.6 (0.7–3.5)
McCredie *et al.* (1994), Australia	Case–control (82 cases vs. 164 controls)	Cases: Central Cancer Registry Controls: Electoral polls	1985–1989	0–14 years	Years of father's schooling (tertiles)	All: OR (first vs. other) OR=1.1 (0.6–1.8)
Savitz and Ananth (1994), USA	Case–control (241 cases vs. 212 controls)	Cases: Denver Standard Metropolitan Statistical Area Controls: random digit dialing; matching by age (±3 years) and sex	1976–1983	<15 years	Age at diagnosis, year of diagnosis, sex, race, residential stability, mother's age, mother's smoking during pregnancy, father's education, annual per capita income, wire code	OR=0.9 (0.5–1.8) – 2–3 child OR=0.7 (0.2–2.5) – ≥fourth child
Linet *et al.* (1996), Sweden	Case–control (570 cases vs. 2850 controls)	Cases: linked and ascertained by National Cancer Registers and Medical Birth Register Controls: randomly selected from Medical Birth Register and Cause of Death Registries	1973–1989	<15 years	Sex, birth year and month, and surviving without a diagnosis of brain tumor to the date of diagnosis for the matched case	Total: OR=1.2 (1.0–1.5) – first child vs. ≥second child Low-grade astrocytoma: 1.0 (0.7–1.3) High-grade astrocytoma: 1.6 (0.9–2.8) Medulloblastoma: OR=1.4 (0.9–2.2) Ependymoma: OR=1.4 (0.8–2.5) Others: OR=1.2 (0.9–1.7)
Heuch *et al.* (1998), Norway	Cohort (*n*=459 brain tumors and 1 489 297 children)	Cases: ascertained via linkage of Norwegian Cancer Registry and Medical Birth Registry	1967–1992	<15 years	Sex and age (in four intervals)	All: OR (95% CI) first child as reference 1.06 (0.85–1.31) – second 1.06 (0.84–1.34) – ≥third Medulloblastoma: 0.94 (0.56–1.59) – second 1.05 (0.60–1.84) – ≥third Astrocytoma: 1.19 (0.84–1.69) – second 1.11 (0.75–1.64) – ≥third
Schüz *et al.* (2001), Germany	Case–control (446 cases vs. 2458 controls)	Cases: German's Children Cancer Registry Controls: local offices for registration of residents	1993–1997	<15 years	Sex, age groups of 1 year, and year of birth, degree of urbanization and socioeconomic status	All: OR (95% CI) >first child as reference 1.06 (0.86–1.30) – first child Astrocytoma: 1.16 (0.78–1.73) Ependymoma: 0.98 (0.54–1.78) Medulloblastoma: 1.21 (0.81–1.80)

Table 1 (***continued***)

References, countries	Study design – sample size	Sources of population	Study period	Age at diagnosis	Covariates	Results (estimates and 95% CI)
Mogren *et al.* (2003), Sweden	Cohort (237 cases, *n*=248 701)	Cases: identified and ascertained by Swedish Cancer Registry	1955–1990	<15 years	NA	All tumors: first child as reference RR=1.15 (0.75–1.70) – 2–3 child 0.74 (0.15–2.16) – ≥fourth child Low-grade astrocytoma: RR=1.00 (0.70–1.38) – 2–3 child 1.15 (0.49–2.26) – ≥fourth child High-grade astrocytoma: RR=0.97 (0.48–1.730) – 2–3 child 0.72 (0.08–2.62) – ≥fourth child
Shaw *et al.* (2006), Canada	Case–control (272 cases vs. 272 controls)	Cases: tertiary care centers designated by governmental policy to hospitalize and treat children with cancer in the province of Quebec, Canada Controls: Quebec provincial health insurance agency files	1980–1989	<15 years	Mother's level of education	All tumors: OR=1.3 (0.8–2.1) – 1 child 1.4 (0.9–2.3) – ≥2 child
Mallol-Mesnard *et al.* (2008), France	Case–control (209 cases vs. 1681 controls)	Cases: National Registry of Childhood Hematological Cancers (RNHE) and the National Registry of Childhood Solid Tumors (RNTSE) Controls: randomly selected from the French national population representatives	2003–2004	0–14 years	Age and sex	All CNS: OR (95% CI) 1.3 (0.9–1.8) – second 0.8 (0.5–1.2) – ≥third Ependymoma: 1.3 (0.6–2.8) – second 0.7 (0.3–2.0) – ≥third Embryonal tumors: 1.9 (1.2–2.9) – second 1.0 (0.6–1.9) – ≥third Astrocytomas: OR=1.3 (0.6–3.0) – second 0.4 (0.1–1.6) – ≥third Other gliomas: 0.7 (0.4–1.4) – second 0.8 (0.3–1.7) – ≥third
Harding *et al.* (2009), UK, Wales, Scotland	Case–control (576 cases vs. 6276 controls)	Cases: UK Childhood Cancer Study Controls: randomly selected and matched on age and sex from the Family Health Services Authority		≤15 years	Deprivation (socioeconomic status) according to Townsend category quintiles based on address at (pseudo) diagnosis	All CNS tumors: OR (95% CI) 1.08 (0.89–1.32) – second 1.01 (0.80–1.28) – third All gliomas: 1.03 (0.80–1.34) – second 0.88 (0.64–1.21) – third PNET/medulloblastoma: 1.24 (0.82–1.87) – second 1.30 (0.81–2.09) – third Pilocytic astrocytoma: 1.01 (0.70–1.47) – second 0.84 (0.53–1.34) – ≥third
Schmidt *et al.* (2010), Denmark, Norway, Sweden, Finland	Case–control (3983 cases vs. 71 488 controls)	Cases: childhood cancer registries (Sweden and Denmark) and solid-tumor database (Norway)	1985–2006	<15 years	Birth weight and gestational age	Embryonal CNS: OR (95% CI) 0.96 (0.79–1.17) – second 0.85 (0.65–1.13) – third 0.89 (0.62–1.30) – ≥fourth

Table 1 (***continued***)

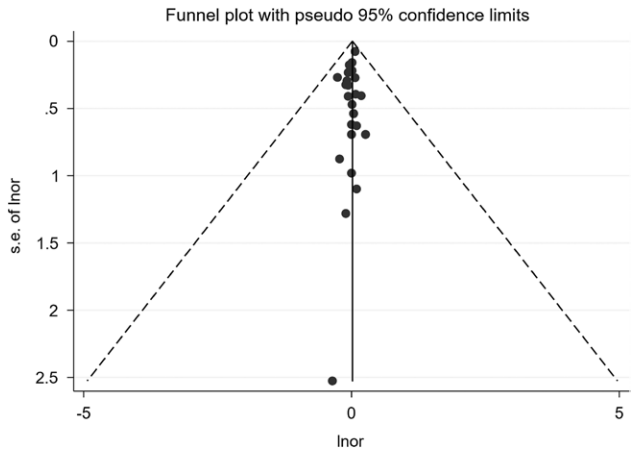
References, countries	Study design – sample size	Sources of population	Study period	Age at diagnosis	Covariates	Results (estimates and 95% CI)
		Controls: were matched individually by age (birth month and year), sex, and country to five controls; randomly selected from the national population registries				Other gliomas: 1.03 (0.76–1.40) – second 0.95 (0.64–1.42) – third 0.99 (0.91–1.07) – ≥fourth Other specified tumors: 1.10 (0.81–1.39) – second 0.83 (0.53–1.15) – third 1.15 (0.90–2.12) – ≥fourth Other unspecified tumors: 0.70 (0.50–0.98) – second 0.81 (0.51–1.21) – third 0.85 (0.45–1.63) – ≥fourth
MacLean *et al.* (2010), USA	Case–control (3793 cases vs. 14 932 controls)	Cases California Cancer Registry and confirmed via linkage with California Office of Vital Records' live birth certificate database Controls: matched on date of birth and sex, randomly selected (4: 1) from California birth certificate database	1988–2006	<15 years	Birth weight and birth order, the matching factors (date of birth and sex), race, ethnicity, maternal age, and maternal education	All brain tumors: OR=1.01 (0.90–1.12) – second 1.07 (0.93–1.22) – third 0.90 (0.76–1.05) – ≥fourth Low-grade glioma: 0.92 (0.77–1.11) – second 0.94 (0.75–1.18) – third 0.75 (0.56–0.99) – ≥fourth High-grade glioma: 1.32 (1.01–1.72) – second 1.32 (0.96–1.72) – third 1.36 (0.95–1.96) –≥fourth Medulloblastoma: 0.93 (0.70–1.25) – second 1.05 (0.72–1.54) – third 0.95 (0.62–1.45) – ≥fourth PNET: 1.14 (0.81–1.62) – second 0.92 (0.58–1.46) – third 1.10 (0.65–1.84) – ≥fourth Germ cell: 1.10 (0.63–1.94)-second 1.23 (0.63–2.42) – third 0.58 (0.23–1.50) – ≥fourth Ependymoma: 0.99 (0.68–1.45) – second 1.07 (0.66–1.71) – third 0.91 (0.52–1.60) – ≥fourth
Von Behren *et al.* (2011), USA	Case–control (17 672 cases vs. 49 236 controls)	–	California: 1988–1997 Minnesota: 1988–2004 New York: 1985–2001 Texas: 1990–1998 Washington: 1980–2004	28 days to 4 years 28 day to –14 years 28 day to 14 years 28 day to 14 years 28 day to 14 years	Matching and pooling variables (state, sex, year of birth), maternal race, maternal age, singleton vs. multiple birth, gestational age and birth weight	All CNS: 1.01 (0.93–1.09) – second 0.85 (0.77–0.95) – third 0.77 (0.68–0.89) – ≥fourth Ependymoma and choroid plexus 0.97 (0.77–1.23) – second 0.71 (0.51–0.89) – third 0.62 (0.41–0.95) – ≥fourth

Table 1 (*continued*)

References, countries	Study design – sample size	Sources of population	Study period	Age at diagnosis	Covariates	Results (estimates and 95% CI)
						Astrocytoma: 0.98 (0.87–1.10) – second 0.79 (0.67–0.92) – third 0.72 (0.59–0.88) – ≥fourth Intracranial embryonal: 0.99 (0.84–1.16) – second 0.96 (0.78–1.18) – third 0.93 (0.72–1.20) – ≥fourth Other gliomas: 1.21 (0.97–1.50) – second 1.05 (0.79–1.39) – third 0.76 (0.52–1.10) – ≥fourth
Oksuzyan *et al.* (2013), USA	Case–control (3308 cases vs. 3308 controls)	Cases: California Cancer Registry Controls: randomly selected from the California Birth Registry and matched to cases (1: 1) on the basis of date of birth (6 months) and sex	1988–2008	<15 years	Child's race, gestational age, father's education, mother's age, and source of payment for delivery	OR=0.92 (0.79–1.06)
Greenop *et al.* (2014), Australia	Case–control (335 cases vs. 1363 controls)	Incident cases: 0 pediatric oncology centers in Australia Controls: random digit dialing, Matched by: child's age at diagnosis or recruitment (controls), sex and state of residence	2005–2010	<15 years	Maternal age, child's year of birth group, child's ethnicity, and maternal pre-pregnancy folate supplementation	All brain tumors: 1.0 (0.7–1.3) – second 1.0 (0.7–1.4) – ≥third Low-grade gliomas 1.1 (0.7–1.6) – second 1.1 (0.7–1.8) – ≥third High-grade gliomas 0.8 (0.5–1.5) – second 0.8 (0.4–1.6) – ≥third
Schüz *et al.* (2015), Denmark	Cohort (1469 cases, *n*=2 461 283)	Cases: Danish Cancer Registry and Danish Medical Birth Registry	1973–2010	0–14 years	Birth weight and parental age at the child's birth	CNS tumors: OR (95% CI) 0.96 (0.86–1.08) – second 0.91 (0.77–1.08) – third 1.02 (0.92–1.02) – ≥fourth 0.98 (0.92–1.04) – Linear
De Paula Silva *et al.* (2016), Brazil	Case–control (340 cases vs. 1580 controls)	Cases national cancer registries Controls: systematic randomly selected from Brazil's Live Birth Information System (4: 1), matched by birth year and sex	2000–2010	0–14 years	Maternal education, sex, birth weight, and birth anomalies	Embryonal tumors: OR=0.96 (0.73–1.25) first vs. ≥second child (as reference group) Embryonal tumors – diagnosed ≤24 months OR=0.82 (0.57–1.17) first vs. ≥second child Embryonal tumors – diagnosed >24 months OR=1.13 (0.79–1.61) first vs. ≥second child
Vienneau *et al.* (2016), Denmark, Sweden, Norway, and Switzerland	Case–control (352 cases vs. 646 controls)	Cases: unequivocal diagnostic imaging Controls: population registries Matched by age, sex, and geographical region	2004–2008	7–19 years	Maternal age and parental education	1.04 (0.68–1.20) – ≥second child

CI, confidence interval; CNS, central nervous system; OR, odds ratio; NA, not applicable; PNET, primitive neuroectodermal tumor; RR, relative risk.

Fig. 3



Funnel plot to evaluate publication bias of included case–control studies in the current meta-analysis.

Our findings are consistent with several large case–control studies (MacLean *et al.*, 2010; Von Behren *et al.*, 2011; Oksuzyan *et al.*, 2013) and a cohort study by Schüz *et al.* (2015). For example, in a case–control study of 3793 cases and 14 932 controls using data from California Cancer Registry, MacLean *et al.* (2010) showed that compared with first birth order, the association between second, third, and fourth birth order and higher and all CBT were 1.01 (95% CI: 0.90–1.12), 1.07 (0.93–1.22), and 0.90 (0.75–1.05), respectively. The null association was consistent in both stratified analysis (i.e. low grade vs. high-grade glioma) and histologic subtypes (i.e. medulloblastoma, ependymoma, or germ cell) (MacLean *et al.*, 2010). Similarly, in a cohort study of 1499 incident cases among 2 461 283 study participants in Denmark, Schüz *et al.* (2015) did not find an association between birth order and the risk of central nervous system. The hazard ratios for second, third, and fourth order or higher order of birth, compared with first order of birth, were 0.98 (95% CI: 0.86–1.08), 0.91 (0.77–1.08), and 0.98 (0.92–1.02), respectively.

The stratified analysis by age at diagnosis shows that although age was included in the multivariable model, there was a small but significant inverse association between birth orders and CBTs, whereas there was a positive association without controlling for age at diagnosis in the multivariable model. It appeared that age at diagnosis might be a confounder; however, the underlying mechanisms need to be elucidated, given the fact that there is no clear trend in the risk of CBT across age group. We, however, consider that age at diagnosis be given more weight in the adjusted results.

Mechanistically, birth order might be a marker of infectious exposures in which higher order children might have higher exposure to infectious agents than lower order children. For example, Greaves (2001), proposed that delayed exposure to infectious agents might cause an abnormal response after a common infection, thus increasing possibility of the second mutation and leading to acute lymphocytic leukemia. In this particular disease, it appears that immune response may play an important role in cancer risk. It should be noted that the association between birth order and infectious agents might be diluted owing to the large interval of birth or once the child had infections from other sources such as day care (Perrillat *et al.*, 2002; Gilham *et al.*, 2005; Ma *et al.*, 2005). While recognizing the importance of this information, we were not be able to obtain such information.

Another mechanism is that birth order might be a marker for early exposure to estrogen, which plays an important role in later development of cancer (Ekbom, 1998). Estrogen levels in maternal and umbilical cord blood were found to be higher in first pregnancies compared with second or higher order pregnancies (Maccoby *et al.*, 1979; Bernstein *et al.*, 1986; Panagiotopoulou *et al.*, 1990). By this hormonal-related mechanisms, birth order was found to be related with several adult cancers, such as testicular cancer (reduced risk) (Richiardi *et al.*, 2004; Cook *et al.*, 2008) or adult glioma (reduced risk) (Amirian *et al.*, 2010).

The other mechanism is that higher birth order children might have higher levels of microchimerism (Adams and Nelson, 2004). In other words, transportation of cells between mother and fetus during pregnancy has been reported (Srivatsa *et al.*, 2003) with the potential of retention of maternal cells in children remains for decades (Maloney *et al.*, 1999). This microchimeric mechanism may pose different levels of susceptibility to diseases by birth order such as chronic lymphocytic leukemia and lymphoproliferative disease (Adams and Nelson, 2004; Gadi, 2007; Jønsson *et al.*, 2007). There are, however, limited epidemiologic data to support this hypothesis and thus warrant for further studies.

One of the most important challenges in the current meta-analysis is the heterogeneity of the disease. Indeed, the central nervous system tumors have more than 100 histologic subtypes. Even though there are several main histologic subtypes of CBTs (i.e. astrocytoma, ependymoma, medulloblastoma, or gliomas, both low grade and/or high grade), we could not perform stratified analysis by those subtypes owing to the small number of studies that contain complete estimates for such analysis. Another difficulty is the incompleteness and difference in methods used for case ascertainment at different cancer registries. The other challenge is that different cancer registries vary one to the other regarding when to report or record benign brain tumors. For example, the reporting of nonmalignant tumors is not required by law, thus such type of data is limited before 2004 (Johnson *et al.*, 2014).

Table 2 Stratified analysis of the association between birth order and risk of childhood brain tumors in the current meta-analysis

			Heterogeneity test		
Stratification group	References	OR (95% CI)	*Q*	*P*	I^2 (%)[a]
Geographic region					
Total	–	1.01 (0.98–1.03)	43.84	0.01	45.3
USA, Canada	Kuijten *et al*., 1990; Emerson et al., 1991; 1991. Shaw *et al*., 2006; MacLean *et al*., 2010; Von Behren *et al*., 2011; Oksuzyan *et al*., 2013	1.01 (0.97–1.03)	45.33	<0.001	80.10
Europe	Savitz and Ananth, 1994; Linet *et al*., 1996; Schüz *et al*., 2001; Mogren *et al*., 2003; Mallol-Mesnard *et al*., 2008; Harding *et al*., 2009; Schmidt *et al*., 2010; Schüz *et al*., 2015; Vienneau *et al*., 2016	0.97 (0.92–1.03)	8.37	0.68	0.00
Australia and Brazil	McCredie *et al*., 1994; Greenop *et al*., 2014; de Paula Silva *et al*., 2016	1.02 (0.85–1.19)	0.12	0.99	0.00
Adjusting for age at diagnosis					
Yes	Emerson *et al*., 1991; Savitz and Ananth, 1994; Linet *et al*., 1996; Schüz *et al*., 1999; Mogren *et al*., 2003; Mallol-Mesnard *et al*., 2008; MacLean *et al*., 2010; Schmidt *et al*., 2010; Von Behren *et al*., 2011; Greenop *et al*., 2014; Schüz *et al*., 2015	0.94 (0.91–0.98)	30.52	0.33	41.00
No	Kuijten *et al*., 1990; Emerson *et al*., 1991; McCredie *et al*., 1994; Shaw *et al*., 2006; Harding *et al*., 2009; de Paula Silva *et al*., 2016; Vienneau *et al*., 2016	1.07 (1.03–1.11)	0.40	0.99	0.00

CI, confidence interval; OR, odds ratio.
[a]I^2: proportion of total variation across studies owing to heterogeneity.

However, it is unclear whether incomplete ascertainment would generate a bias with respect to birth order results.

In addition, one limitation in the current meta-analysis is the availability of few prospective cohort studies. Consequently, we could only perform an analysis to determine the association between first order and CBTs in comparison with second or higher birth order. The other limitation is that there might be a potential residual confounding in our meta-analysis. For example, family size is correlated with social economic status in many countries.

Conclusion

We found no overall association between birth order and CBT in both case–control and cohort study designs. Given the secular trend toward smaller number of children, our results, if confirmed, might explain part of the increasing incidence of brain tumors (less fourth birth order children in the population). This small association observed for fourth birth order in case–control studies deserves further consideration. Limited statistical power might have hampered the results of the analyses of cohort studies.

Acknowledgements

This work is supported by NIH/NCI grant # 1P20CA210300-01 (PI: X.O. Shu and T.V. Tran) and the University of Pittsburgh Medical Center Hillman Cancer Center start-up grant (PI: H.N. Luu) to Hung N. Luu.

Conflicts of interest

There are no conflicts of interest.

References

Adams KM, Nelson JL (2004). Microchimerism: an investigative frontier in autoimmunity and transplantation. *JAMA* **291**:1127–1131.

Amirian E, Scheurer ME, Bondy ML (2010). The association between birth order, sibship size and glioma development in adulthood. *Int J Cancer* **126**:2752–2756.

Bernstein L, Depue RH, Ross RK, Judd HL, Pike MC, Henderson BE (1986). Higher maternal levels of free estradiol in first compared to second pregnancy: early gestational differences. *J Natl Cancer Inst* **76**:1035–1039.

Cook MB, Graubard BI, Rubertone MV, Erickson RL, McGlynn KA (2008). Perinatal factors and the risk of testicular germ cell tumors. *Int J Cancer* **122**:2600–2606.

De Paula Silva N, de Souza Reis R, Garcia Cunha R, Pinto Oliveira JF, Santos MO, Pombo-de-Oliveira MS, de Camargo B (2016). Maternal and birth characteristics and childhood embryonal solid tumors: a population-based report from Brazil. *PLoS One* **11**:e0164398.

De Robles P, Fiest KM, Frolkis AD, Pringsheim T, Atta C, St Germaine-Smith C, *et al*. (2015). The worldwide incidence and prevalence of primary brain tumors: a systematic review and meta-analysis. *Neuro Oncol* **17**:776–783.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials* **7**:177–188.

Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**:629–634.

Ekbom A (1998). Growing evidence that several human cancers may originate in utero. *Semin Cancer Biol* **8**:237–244.

Emerson JC, Malone KE, Daling JR, Starzyk P (1991). Childhood brain tumor risk in relation to birth characteristics. *J Clin Epidemiol* **44**:1159–1166.

Gadi VK (2007). Chronic lymphocytic lymphoma: another example of parental favoritism? *Leuk Lymphoma* **48**:2306–2307.

Gilham C, Peto J, Simpson J, Roman E, Eden TOB, Greaves MF, Alexander FE, UKCCS Investigators (2005). Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case–control study. *BMJ* **330**:1294.

Greaves MF (2001). Commentary: birth order and risk of childhood acute lymphoblastic leukaemia (ALL). *Int J Epidemiol* **30**:1438–1439.

Greenop KR, Blair EM, Bower C, Armstrong BK, Milne E (2014). Factors relating to pregnancy and birth and the risk of childhood brain tumors: results from an Australian case–control study. *Pediatr Blood Cancer* **61**:493–498.

Harding NJ, Birch JM, Hepworth SJ, McKinney PA (2009). Infectious exposure in the first year of life and risk of central nervous system tumors in children: analysis of day care, social contact, and overcrowding. *Cancer Causes Control* **20**:129–136.

Heuch JM, Heuch I, Akslen LA, Kvåle G (1998). Risk of primary childhood brain tumors related to birth characteristics: a Norwegian prospective study. *Int J Cancer* **77**:498–503.

Higgins JPT, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**:1539–1558.

Johnson KJ, Cullen J, Barnholtz-Sloan JS, Ostrom QT, Langer CE, Turner MC, *et al*. (2014). Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. *Cancer Epidemiol Biomarkers Prev* **23**:2716–2736.

Jønsson V, Tjønnfjord G, Samuelsen SO, Johannesen T, Olsen J, Sellick G, *et al*. (2007). Birth order pattern in the inheritance of chronic lymphocytic leukaemia and related lymphoproliferative disease. *Leuk Lymphoma* **48**:2387–2396.

Kuijten RR, Bunin GR, Nass CC, Meadows AT (1990). Gestational and familial risk factors for childhood astrocytoma: results of a case–control study. *Cancer Res* **50**:2608–2612.

Linet MS, Gridley G, Cnattingius S, Nicholson HS, Martinsson U, Glimelius B, *et al.* (1996). Maternal and perinatal risk factors for childhood brain tumors (Sweden). *Cancer Causes Control* **7**:437–448.

Ma X, Buffler PA, Wiemels JL, Selvin S, Metayer C, Loh M, *et al.* (2005). Ethnic difference in daycare attendance, early infections, and risk of childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev* **14**: 1928–1934.

Maccoby EE, Doering CH, Jacklin CN, Kraemer H (1979). Concentrations of sex hormones in umbilical-cord blood: their relation to sex and birth order of infants. *Child Dev* **50**:632–642.

MacLean J, Partap S, Reynolds P, von Behren J, Fisher PG (2010). Birth weight and order as risk factors for childhood central nervous system tumors. *J Pediatr* **157**:450–455.

Mallol-Mesnard N, Menegaux F, Lacour B, Hartmann O, Frappaz D, Doz F, *et al.* (2008). Birth characteristics and childhood malignant central nervous sytem tumors: the ESCALE study (French Society for Childhood Cancer). *Cancer Detect Prev* **32**:79–86.

Maloney S, Smith A, Furst DE, Myerson D, Rupert K, Evans PC, Nelson JL (1999). Microchimerism of maternal origin persists into adult life. *J Clin Invest* **104**:41–47.

McCredie M, Maisonneuve P, Boyle P (1994). Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. *Int J Cancer* **56**:11–15.

McCredie M, Little J, Cotton S, Mueller B, Peris-Bonet R, Choi NW, *et al.* (1999). SEARCH international case–control study of childhood brain tumours: role of index pregnancy and birth, and mother's reproductive history. *Paediatr Perinat Epidemiol* **13**:325–341.

McKean-Cowdin R, Razavi P, Barrington-Trimis J, Baldwin RT, Asgharzadeh S, Cockburn M, *et al.* (2013). Trends in childhood brain tumor incidence, 1973–2009. *J Neurooncol* **115**:153–160.

Mogren I, Malmer B, Tavelin B, Damber L (2003). Reproductive factors have low impact on the risk of different primary brain tumours in offspring. *Neuroepidemiology* **22**:249–254.

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* **339**:b2535.

Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Kheifets L (2013). Birth weight and other perinatal factors and childhood CNS tumors: a case–control study in California. *Cancer Epidemiol* **37**:402–409.

Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS. (2017). CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro Oncol* **19**:v1–v88.

Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D (1990). Maternal age, parity, and pregnancy estrogens. *Cancer Causes Control* **1**:119–124.

Perrillat F, Clavel J, Auclerc MF, Baruchel A, Leverger G, Nelken B, *et al.* (2002). Day-care, early common infections and childhood acute leukaemia: a multicentre French case–control study. *Br J Cancer* **86**:1064–1069.

Richiardi L, Akre O, Lambe M, Granath F, Montgomery SM, Ekbom A (2004). Birth order, sibship size, and risk for germ-cell testicular cancer. *Epidemiology* **15**:323–329.

Savitz DA, Ananth CV (1994). Birth characteristics of childhood cancer cases, controls, and their siblings. *Pediatr Hematol Oncol* **11**:587–599.

Schmidt LS, Kamper-Jørgensen M, Schmiegelow K, Johansen C, Lähteenmäki P, Träger C, *et al.* (2010). Infectious exposure in the first years of life and risk of central nervous system tumours in children: analysis of birth order, childcare attendance and seasonality of birth. *Br J Cancer* **102**:1670–1675.

Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J (1999). Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol* **28**:631–639.

Schüz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J (2001). Risk factors for pediatric tumors of the central nervous system: results from a German population-based case–control study. *Med Pediatr Oncol* **36**:274–282.

Schüz J, Luta G, Erdmann F, Ferro G, Bautz A, Simony SB, *et al.* (2015). Birth order and risk of childhood cancer in the Danish birth cohort of 1973–2010. *Cancer Causes Control* **26**:1575–1582.

Shaw AK, Li P, Infante-Rivard C (2006). Early infection and risk of childhood brain tumors (Canada). *Cancer Causes Control* **17**:1267–1274.

Srivatsa B, Srivatsa S, Johnson KL, Bianchi DW (2003). Maternal cell microchimerism in newborn tissues. *J Pediatr* **142**:31–35.

Vienneau D, Infanger D, Feychting M, Schüz J, Schmidt LS, Poulsen AH, *et al.* (2016). A multinational case–control study on childhood brain tumours, anthropogenic factors, birth characteristics and prenatal exposures: a validation of interview data. *Cancer Epidemiol* **40**:52–59.

Von Behren J, Spector LG, Mueller BA, Carozza SE, Chow EJ, Fox EE, *et al.* (2011). Birth order and risk of childhood cancer: a pooled analysis from five US States. *Int J Cancer* **128**:2709–2716.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* **335**:806–808.

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P (2013). The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: *http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp*. [Accessed 2 July 2018]