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Birth weight and risk of neuroblastoma: a meta-analysis

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8 **Birth weight and risk of neuroblastoma: a meta-analysis**
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Abstract

Background Neuroblastoma is the most common solid tumor in infancy but its etiology is largely unknown. Prenatal factors might play a key role in its pathogenesis. Previous studies investigated whether birth weight is associated with risk of neuroblastoma, with conflictive results. We conducted a meta-analysis to quantitatively summarize the published evidence.

Methods Results from ten case-control studies and one cohort study (1966 – December 2008) were included, involving a total of 3,004 children with neuroblastoma. We constructed random-effects and fixed-effects models, performed “pool-first” analyses, assessed heterogeneity and publication bias and performed sensitivity and influence analyses.

Results High birth weight (>4,000g) was associated with increased risk of neuroblastoma (odds ratio (OR): 1.19 ; 95% confidence interval (95%CI): 1.04-1.36). Results for high birth weight were highly homogenous ($I^2=0\%$). Low birth weight (<2,500g) was also related to increased risk of neuroblastoma (OR: 1.24; 95%CI: 1.0-1.55), but results were more heterogeneous ($I^2=30\%$). No evidence for particularly influential studies or for publication bias was found. However, sensitivity analysis indicated the presence of bias in studies on the association with low birth weight. Above 2,500g each 1000g-increase in birth weight was associated with a 13% (95% CI: 3-25%) increase in risk of neuroblastoma.

Conclusions This meta-analysis shows that high birth weight is highly reproducibly associated with increased risk of neuroblastoma. The association with low birth weight was found to be less robust and deserves further studies.

Keywords Birth weight, neuroblastoma, children, infants, meta-analysis

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3 **Key messages**
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5 The etiology of neuroblastoma is largely unknown, but prenatal factors have been suggested
6 to play a key role in its pathogenesis.
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10 This meta-analysis shows that high birth weight is consistently associated with an increased
11 risk of neuroblastoma across studies.
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15 Low birth weight is also associated with increased neuroblastoma risk, but the results are
16 more heterogenous.
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For Review Only

Introduction

Neuroblastoma, a solid tumor arising from primitive sympathetic neural precursor cells, has an incidence rate of about 40 per million infants in the first year of life, thereby being the most common malignancy in infancy.¹ It has been termed a „clinical enigma“ of cancer research because of its hard-to-predict biological behaviour, spanning from spontaneous regression to very rapid metastatic spread, thereby making diagnosis, therapy and prognosis difficult.² Efforts to establish measures of secondary prevention like newborn screening for vanillylmandelic acid in urine gave controversial results.^{3,4}

Importantly, no clear-cut risk factor for neuroblastoma has been identified to far. Because of its appearance very early in life it has been suggested that risk factors which act prenatally could play a role in the pathogenesis of neuroblastoma. However, conflictive data have been accumulated over the past years on such factors like exposure to maternal smoking,⁵ maternal medication⁶ or vitamins during pregnancy,⁷ possibly arising from the relatively small number of studies performed so far, or from the difficulties to correctly obtain the respective exposures during pregnancies.

An alternative attempt is to focus on indicators of exposures which can be easily obtained in large samples with little bias and are established markers of the intrauterine environment.

Birth weight can be considered to be such a marker. It is routinely obtained at birth by trained personnel with little systematic error and is generally collected in medical records or registries.⁸ Studies suggest that environmental factors such as maternal nutrition and maternal diseases are important for birth weight.^{9,10} In the past, a number of investigators have studied birth weight in infants and children with neuroblastoma.¹¹⁻¹³ A recent narrative review came to the conclusion that there might be an association of neuroblastoma risk with low birth

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3 weight.¹⁴ Here, we aimed to quantify the association and performed a meta-analysis on the
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5 relation between birth weight and risk of neuroblastoma.
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8 9 10 **Methods**

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12 We performed a comprehensive literature search according to the MOOSE guidelines for
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14 meta-analyses of observational studies,¹⁵ including the databases MEDLINE (1966 –
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16 December 2008) and EMBASE (1989 – December 2008) to identify studies that investigated
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18 the association between birth weight and risk of neuroblastoma, using the terms “birth
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20 weight” and “neuroblastoma”. The entire search was performed in the fulltext option, without
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22 language restrictions. Furthermore, we manually searched all references cited in original
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24 studies and reviews identified.
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31 To be eligible, a study had to fulfil the following criteria, defined a priori: 1) It had to be an
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33 original report on birth weight and risk of neuroblastoma, and 2) odds ratios (OR) and 95%
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35 confidence intervals (95% CI, or data with which to calculate them) for risk of neuroblastoma
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37 in at least two strata of birth weight had to have been presented. Alternatively, an odds ratio
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39 and 95% CI for the change in neuroblastoma risk per unit change in birth weight had to have
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41 been reported. If only data for risk ratio were reported (cohort studies), they were used for
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43 pooling since under the rare-disease assumption OR and risk ratio are nearly equal.¹⁶ The
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45 course of the systematic literature review is illustrated in Figure 1.
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52 From all studies included, data were abstracted in duplicate, using a standardized form. The
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54 following study characteristics were extracted: publication year, country, region, study design,
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56 year of birth, age at diagnosis, study size, matching ratio (if case-control study), matching
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58 variables (if case-control study), source of controls (if case-control study), source of case
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60 diagnosis, source of data for birth weight, effect measures and confounders. An independent

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3 reviewer confirmed all data entries.
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8 Three different meta-analytic approaches were used: 1) A birth weight cutoff of 4,000 g (high
9 birth weight) ¹⁷ was used to compare risks of neuroblastoma above and below this value
10 (dichotomous comparison). 2) The dichotomous approach was repeated for a birth weight
11 cutoff of 2,500 g (low birth weight). ¹⁷ 3) The pool-first method ¹⁸ was used to combine
12 regression coefficients obtained from the studies for trend analysis.
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21 For dichotomous comparisons, we extracted data on numbers of subjects with and without
22 neuroblastoma above or below the cutoff value and calculated corresponding crude ORs and
23 95% CIs. We constructed both fixed-effects and random-effects models to estimate the pooled
24 ORs for risk of neuroblastoma above versus below the respective cutoff value across all
25 studies.
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36 To studies that provided data for more than two categories of birth weight, we applied the
37 ‘pool-first method’ to quantify the dose-response relationship between birth weight and risk
38 of neuroblastoma. This method, as introduced by Greenland and Longnecker, ¹⁸ allows the
39 meta-analytic pooling of regression data, but accounts for the fact that estimates used to
40 calculate single regression coefficients are correlated to each other within one study. This
41 problem is solved by firstly pooling the data within each study (“pool first”) to obtain
42 respective regression coefficients for each study, followed by pooling these regression
43 coefficients. The resulting pooled regression coefficient can be interpreted like a regression
44 coefficient from a single study. Visual inspection of the plots of eleven out of the twelve
45 individual studies revealed a u-shaped relation between birth weight and risk of
46 neuroblastoma. For each of these studies a study-specific linear and a quadratic regression
47 coefficient and corresponding 95% CIs were calculated using a log-quadratic model.
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3 Following the pool-first approach,¹⁸ the resulting linear and quadratic regression coefficients
4 and their 95% CIs were pooled using a random-effects model. After having performed the
5 sensitivity analyses (see below), we repeated the pool-first analysis, now applying a linear
6 model restricted to the birth weight spectrum above 2,500g and to studies that used registries
7 to obtain birth weight data.
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17 Heterogeneity of study results was assessed by calculating the I^2 , as proposed by Higgins et
18 al.¹⁹ I^2 , ranging from 0-100%, is a direct measure of inconsistency of study results in a meta-
19 analysis. Robustness of the pooled estimate was checked by influence analysis, using a
20 random-effects model: each of the study estimates was individually omitted from the data set,
21 followed in each case by re-calculation of the pooled estimate of the remaining studies.
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31 Four different subgroup analyses were performed to identify potential sources of
32 heterogeneity between study results. First, we calculated separate estimates for all studies
33 from North America (U.S. and Canada) and for studies from Europe. Second, we stratified all
34 studies according to method of obtaining birth weight (registry/certificate vs interview).
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41 Third, subgroup estimates were calculated according to method of obtaining case diagnosis
42 (registry vs others). Fourth, we stratified all studies according to source of controls
43 (registry/certificate vs others). For all analyses, a random-effects model was used.
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51 Publication bias was assessed by inspection of the funnel plot, and formal testing for funnel
52 plot asymmetry using Begg's test and Egger's test.
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57 All calculations were performed using STATA 8 (Stata corporation, College Station, TX,
58 USA).
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Results

During the systematic review, we identified 13 studies which provided data on birth weight and subsequent risk of neuroblastoma. One study²⁰ had to be excluded since only an adjusted OR was reported for neuroblastoma after high birth weight (OR: 1.40; 95% CI: 0.90-2.20; adjusted for maternal age, birth order, weeks of gestation and sex) and an unadjusted OR could not be calculated from the data. Another study¹² had to be excluded since case overlap to a previous study²¹ was substantial. Thereby, a total of eleven studies could be used for meta-analysis (Figure 1).^{11, 13, 21-29} Study characteristics of included reports are shown in Table 1. Studies involved a total of 2,159,927 individuals, of whom 3,004 suffered from neuroblastoma. One study was a cohort study. The remaining eleven studies had a case-control design with matching ratios ranging from 1:1 to 1:10. The first study was published in 1985, while the most recent appeared in 2008. Studies were performed in either the United States, Canada, France, Norway or Germany. Age of participants ranged from 0 to 18 years. Study size ranged from 417 to 2,127,452 participants. In seven of the studies, cases were derived from cancer registries, while in the remaining four studies they came from other sources.

Ten studies provided data for calculation of OR (95% CI) of risk of neuroblastoma in subjects with high birth weight (> 4,000 g), compared to those below this cutoff value. In Figure 2, the forest plot with ORs and 95% CIs and the pooled estimate for risk of neuroblastoma in subjects with high birth weight are shown. High birth weight was associated with increased risk of neuroblastoma. This effect measure was identical when using the random-effects model as well as the fixed-effects model (OR: 1.19; 95% CI: 1.04-1.36). According to I^2 , 0% of the total variation across studies was due to heterogeneity. Influence analysis (random-effects model) showed that the pooled estimate was very robust: Omission of individual study estimates led to pooled ORs ranging from 1.17 (95% CI: 1.01-1.36) to 1.20 (95% CI: 1.04-

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3 1.40). No indication for publication bias was found, as investigated by visual inspection of the
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5 funnel plots (not shown), and Begg's test ($p = 0.28$) and Egger's test ($p = 0.50$).
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10 Ten studies gave data for calculation of OR (95% CI) of risk of neuroblastoma in subjects
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12 with low birth weight ($< 2,500$ g), compared to those above this cutoff value. Figure 3 shows
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14 the forest plot with ORs and 95% CIs and the pooled estimate for risk of neuroblastoma after
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16 low birth weight. Low birth weight was related to increased risk of neuroblastoma by random-
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18 effects model (OR: 1.24; 95% CI: 1.0-1.55) as well as by using the fixed-effects model (OR:
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20 1.24; 95% CI: 1.04-1.50). According to I^2 , 30% of the total variation across studies was due
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22 to heterogeneity. Omission of individual studies revealed that no particular study had a major
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24 influence on the pooled estimate, with pooled ORs ranging from 1.16 (95% CI: 0.97-1.39) to
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26 1.30 (95% CI: 1.04-1.61).
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31 Given these findings of increased risk of neuroblastoma at both ends of the birth weight
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33 spectrum, we repeated the dichotomous comparisons, now using 'normal birth weight' (2500-
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35 4000g) as reference for all studies that gave data on both low and high birth weight ($n = 10$
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37 studies). Pooled estimates after high birth weight (OR: 1.21; 95% CI: 1.05-1.39) as well as
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39 low birth weight remained increased (OR: 1.23; 95% CI: 0.98-1.55).
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45 To quantitatively describe this u-shaped relation between birth weight and risk of
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47 neuroblastoma, we first checked whether the individual studies fulfilled the assumption of a
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49 quadratic model. Since all studies except of one²⁹ did so, we pooled the linear and quadratic
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51 regression coefficients from the remaining eleven single studies obtained by the pool-first
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53 method. Both the linear regression coefficient (0.52; 95% CI: 0.28-0.96) as well as the
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55 quadratic regression coefficient (1.10; 95% CI: 1.01-1.20) were different from 1.0.
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3 To further investigate the association with both high and low birth weight, we performed
4 sensitivity analysis. Regarding the association with high birth weight, region-specific pooled
5 estimates showed no large differences (Table 2). The association with low birth weight was
6 more pronounced in studies from Europe than in those performed in the U.S. or Canada. The
7 method of obtaining data on birth weight did not influence the strength of the association with
8 high birth weight. By contrast, it had a strong effect on the association with low birth weight:
9 Studies which used interview-based data showed a more than 60% increased risk, whereas
10 those which relied on data from registries had a much smaller estimate. While the method of
11 obtaining the case diagnosis had no large effect on neither the estimate for high birth weight,
12 nor on the one for low birth weight, the estimate for low birth weight was strongly influenced
13 by source of controls, with registry-based studies showing smaller effects (Table 2).
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32 Since the sensitivity analysis thereby indicated a considerable bias for low birth weight, we
33 repeated the “pool-first” analysis, now using only birth weight data above 2,500g which came
34 from studies that used registries to obtain birth weight. These data from the individual studies
35 indicated a linear positive relation between birth weight and risk of neuroblastoma above
36 2,500g. Using these data, we therefore calculated linear regression coefficients for the
37 individual studies. Pooling of these linear regression coefficients revealed that above 2,500g,
38 each 1000g-increase in birth weight was associated with a 13% (95% CI: 3-25%) increase in
39 risk of neuroblastoma.
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53 Discussion

54 A number of studies and meta-analyses have shown that birth weight is associated with risk of
55 different types of tumors in infants and children, like leukaemia,³⁰ Wilms’ tumor³¹ and brain
56 tumors.³² Regarding neuroblastoma, however, the evidence appeared to be inconclusive yet.
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This meta-analysis, on first view, indicates that birth weight might be related to

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3 neuroblastoma risk in a u-shaped manner. High birth weight as well as low birth weight are
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5 followed by an increased risk of developing neuroblastoma in later life. However, our
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7 sensitivity analysis gave clear indication for bias in the case of low birth weight, with studies
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9 using interview data reporting stronger associations than those that used registries as data
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11 sources.
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17 Remarkably, the results of this meta-analysis are in some contrast to the conclusions drawn by
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19 authors of the individual studies: In only one of the publications ¹³ it was explicitly
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21 concluded that high birth weight is a risk factor for neuroblastoma, whereas a further three
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23 groups concluded that low birth weight is associated with neuroblastoma. ^{21, 23, 24} In only two
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25 studies, ^{26, 28} the authors concluded that a u-shaped relation exists, as described here. In four
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27 reports it is stated that no association exists with birth weight, ^{22, 25, 27, 29} whereas the authors
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29 of one study did not comment on this issue. ¹¹ At least in some cases, the authors of individual
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31 studies might have overlooked an association with high birth weight, either since it was not
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33 statistically significant, or since the choice of the reference stratum for birth weight might
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35 have “masked” the result (see also Table 1, last column for the original study results as they
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37 were calculated by the authors of the studies).
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46 In addition to the problem of measurement error of birth weight which cannot be fully
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48 disregarded, studies on associations between birth weight and later outcome are prone to
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50 confounding in multiple ways. Adjustment for confounders has been performed in the studies
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52 included here mainly by matching. However, matching was generally restricted to only two
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54 variables, that are, age and gender. In four of the studies, ^{21-23,28} additional adjustments were
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56 made, mainly for socioeconomic status and ethnicity. Adjusted estimates, however, did not
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58 differ largely from the unadjusted results. In only one study, ²⁸ birth weight has been adjusted
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60 for gestational age, which, again, did not change the result. Whereas lack of adjustment leaves

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3 the possibility that the associations observed might also be related to the degree of maturity of
4 the child at birth, such a relation between gestational age and neuroblastoma risk was only
5 present in two of the studies,^{22, 29} but not in the remaining six^{11,13,23,26-28} which investigated
6 this variable.
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15 Although the relation between high birth weight and risk of neuroblastoma was only weak,
16 we observed an unusually high degree of homogeneity between the single study results.
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18 According to I^2 , a meanwhile established indicator of between-study-heterogeneity,¹⁹ 0% of
19 the variation across studies was due to heterogeneity. While, on the one hand, this might
20 indicate a highly constant association between high birth weight and neuroblastoma risk, it
21 might, on the other hand, also raise questions regarding other potential reasons for this
22 extreme between-study homogeneity. Recently, Ioannidis et al. have suggested a number of
23 such potential alternative reasons for this phenomenon.³³ Among them, only the issue of
24 correlated data resulting from studies that came from identical authors or overlapping patient
25 groups is relevant in the context of this meta-analysis. We therefore checked whether there
26 was any overlap in study region or year of diagnosis between the studies and included the
27 relevant information in Table 1. However, we did not find indication that a considerable
28 overlap between any of the study populations could explain our findings. Moreover, influence
29 analysis showed that the effect measure of the relation between high birth weight and risk of
30 neuroblastoma was very robust. The association with high birth weight was also present in the
31 largest study, which is also the only cohort study on this issue,²⁹ supporting the validity of the
32 estimate. Furthermore, in two out of three studies which reported estimates for birth weight >
33 4,500g,^{23,28,29} risk of neuroblastoma was further increased in this category of “very high”
34 birth weight.
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3 Sensitivity analysis indicated that the first notion that low birth weight is also associated with
4 increased risk of neuroblastoma might be biased by maternal recall because interview-based
5 studies gave stronger estimates than studies in which birth weight data came from more
6 objective sources like birth registries and birth records. One might speculate that mothers of
7 children with neuroblastoma and a relatively low birth weight might recall their babies' birth
8 weight even lower than it was. Alternatively, selection bias might have occurred. Interview
9 participation is known to be skewed towards higher socioeconomic status which itself is
10 related to low birth weight.³⁴ This interpretation is further supported by the result of
11 stratification by source of controls. For low birth weight, studies which used methods that
12 required active participation (like telephone interviews) gave higher estimates than those
13 which used less biased sources (like registries) to recruit controls. However, in the three case-
14 control studies which reported response proportions of cases and controls they did not differ
15 greatly in this parameter (cases: 73%, controls: 72%;²³ cases: 69%, controls: 71%;²⁶ cases:
16 80%, controls: 62-69%²¹). Moreover, there are other possible explanations for the observed
17 differences. One might be an under-representation of low-birth-weight children in the control
18 group as discussed by Schuz and Forman,³⁵ which could have caused the results at least in
19 the German study.²¹ Since low education and income are associated with increased risk of
20 low birth weight, as mentioned above, to the extent that the controls have fewer low birth
21 weight infants, an increased OR would result from response bias.

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51 During recent years, it has been suggested that neuroblastoma in infancy and in later
52 childhood represent different entities.³⁶ We therefore additionally checked whether the
53 strength of the association between high birth weight and risk of neuroblastoma differs by age
54 of manifestation. In four of the studies,^{13, 26, 28, 29} results were stratified by age. Interestingly,
55 in three of them the association with high birth weight was stronger in infants below one year
56 of age, as compared to older children. Further studies are needed to investigate whether a
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3 specific subtype of neuroblastoma which manifest in infancy is particularly vulnerable to
4 prenatal influences. Moreover, one has to mention that in none of the studies stage of disease
5 was related to birth weight, leaving the question open whether there is a relation between
6 prenatally acting risk factors and particularly aggressive forms of neuroblastoma.
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15 Since it cannot be assumed that birth weight or fetal growth *per se* is a causal factor leading to
16 later disease risks, as recently again emphasized by Basso,³⁷ the key question concerns the
17 mechanisms underlying associations between high birth weight and risk of neuroblastoma.
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21 Among the factors which stimulate prenatal weight gain maternal diabetes mellitus might be
22 the most prevalent. It is well established that maternal diabetes leads to excess weight gain in
23 utero and, consequently, to increased birth weight,³⁸ as even shown in a randomized trial.³⁹
24 Remarkably, one of the studies included in this meta-analysis showed that maternal diabetes,
25 in particular gestational diabetes, is associated with an increased risk of neuroblastoma in the
26 offspring,²² whereas, however, another study did not observe an association.²³ On the
27 population level, maternal diabetes during pregnancy, particularly gestational diabetes which
28 was estimated to affect up to 14% of pregnant women,⁴⁰ is likely to be the most important
29 risk factor for high birth weight, leading to a 2-3 fold increased risk.⁴¹ Similar applies to
30 maternal overweight during pregnancy. However, it is obvious that one might only speculate
31 whether this proportion is large enough to explain the 19% increase in risk of neuroblastoma
32 after high birth weight.
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53 During recent years some studies have found an increase in the incidence of neuroblastoma in
54 the general population: In Europe, the age-standardized incidence rate for infants increased
55 from 35.4 to 57.8 per million.⁴² It has been discussed that these increases cannot be
56 completely attributed to intensified screening.^{42,43} If the association between high birth
57 weight and neuroblastoma risk exists, it might offer a provocative explanation for this trend
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3 over time since birth weight, as well as the incidence of high birth weight has been increasing
4 continuously in the United States and Europe in recent years, ranging from 6.9%
5 (Switzerland) to 25% increase (Sweden) over the last 20 years in European countries.^{44,45}
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8 However, as in the case of maternal diabetes discussed above, it remains speculative whether
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Taken together, this meta-analysis shows that high birth weight is a risk factor for neuroblastoma. Previous observations that low birth weight is related to increased risk of neuroblastoma¹⁴ might be distorted by bias. However, on the basis of the currently published literature it cannot be excluded that low birth weight is also a risk factor for neuroblastoma, themoreso as data exist showing that rapid early weight gain, which is frequent in low-birth-weight babies, is also associated with increased risk of neuroblastoma.⁴⁶ Further studies on perinatal risk factors for neuroblastoma should focus on maternal diseases and conditions which lead to excessive weight gain during critical periods of early development. If additional studies support the suggestion that gestational diabetes could be an underlying causal factor in this regard, screening for and therapy of gestational diabetes would be a respective preventive measure.

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Conflict of interest

none

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For Review Only

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Table 1 Characteristics of studies on the relation between birth weight and risk of neuroblastoma

Reference	Country	Region	Study design	Year(s) of birth	Year(s) of diagnosis	Age at diagnosis (years)	No. of cases/controls	Matching variables
Bjorge et al. (2008) ²⁹ ***	Norway	nation-wide	cohort	1967-2004	1967-2004	0-15	178/NA (cohort: 2,127,452)	NA
Buck et al (2001) ¹¹	United States	New York	case-control	1971-1987 **	1976-1987	0-5	310/133	Year of birth
Chow et al. (2007) ²²	United States	Washington	case-control	1980-2004	1980-2004	NR	240/2,389	Year of birth
Hamrick et al. (2001) ²³	United States, Canada	nation-wide	case-control	1974-1994 **	1992-1994	0-18	504/504	Age
Johnson and Spitz (1985) ²⁴	United States	Texas	case-control	1949-1978	1964-1978	0-14	148/269	Year of birth
Johnson et al. (2008) ²⁵	United States	Minnesota	case-control	1976-2004	1988-2004	0-14	155/8,712	Year of birth
McLaughlin et al. (2008) ²⁸	United States	New York	case-control	1983-2001	1985-2001	0-14	529/12,010	Place of birth, year of birth
Munzer et al. (2008) ²⁶	France	nation-wide	case-control	1989-2004 **	2003-2004	0-14	190/1,680	Age, gender

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3	Neglia et al. (1988) ²⁷	United States	Minnesota	case-control	NR	NR	0-9	97/388	Year of birth
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6	Schuz et al. (1999) ²¹	Germany	nation-wide	case-control	1978-1994 **	1992-1994	0-14	160/2,577	Age, gender
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10	Uruyama et al. (2007) ¹³	United States	California	case-control	1983-1997	1988-1997	0-4	493/987	Age, gender
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15	NA, not applicable; NR, not reported								
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Table 1 (continued) Characteristics of studies on the relation between birth weight and risk of neuroblastoma

Reference	Source of controls	Source of case-diagnosis	Source of data for birth weight	Original study results
Bjorge et al. (2008) ²⁹	NA (cohort: population)	Cancer registry	Birth registry	Unadjusted risk ratio (95% CI) for birth weight 4,000-4,499g (vs 3,000-3,499g): 1.4 (0.9-2.1); for birth weight < 2,500g: 0.6 (0.2-1.9)
Buck et al (2001) ¹¹	Birth registry	Cancer registry	Birth certificates	Unadjusted OR (95% CI) for birth weight > 4,000g (vs 3,000-3,499g): 1.2 (0.6-2.2); for birth weight < 2,500g: 0.9 (0.4-2.2)
Chow et al. (2007) ²²	Birth certificates	Cancer registry	Birth certificates	OR (95% CI), adjusted for birth year, for birth weight > 4,000g (vs. 2,500-3,999g): 1.25 (0.87-1.79); for birth weight < 2,500g: 0.75 (0.38-1.51)
Hamrick et al. (2001) ²³	Random digit dialing	Clinical records *	Interview	OR (95% CI), adjusted for gender, race, maternal education and household income, for birth weight 4,001-4499g (vs 2,501-4,000g): 1.1 (0.7-1.7); for birth weight 1,500-2,500g: 1.1 (0.6-2.0)
Johnson and Spitz (1985) ²⁴	Birth certificates	Death certificates	Birth certificates	Unadjusted OR (95% CI) for birth weight < 2,500g (vs > 3,800g): 3.22

				(1.13-9.20)
Johnson et al. (2008) ²⁵	Birth registry	Cancer Surveillance	Birth records	Hazard ratio (95% CI), adjusted for sex and birth year, for birth weight > 4,000g (vs 2,500-4,000g): 1.10 (0.70-1.73); for birth weight < 2,500g: 1.17 (0.60-2.28)
McLaughlin et al. (2008) ²⁸	Birth certificates	Cancer registry	Birth certificates	Risk ratio (95% CI), adjusted for birth year, region, gender and race, for birth weight > 4,500g (vs 2,500-3,499g): 1.4 (0.7-2.5); for birth weight < 2,500g: 1.5 (1.0-2.1)
Munzer et al. (2008) ²⁶	Random digit dialing	Cancer registry	Interview	OR (95% CI), adjusted for age and gender, for birth weight > 4,000g (vs 3,000-3,499g): 1.6 (0.9-2.8); for birth weight < 2,500g: 1.8 (0.8-3.8)
Neglia et al. (1988) ²⁷	Birth certificates	Clinical records	Birth certificates	Unadjusted OR (95% CI) for birth weight > 4,000g (vs < 4,000g): 0.96 (0.47-1.73)
Schuz et al. (1999) ²¹	Population	Cancer registry	Interview	OR (95% CI), adjusted for socioeconomic status, for birth weight > 4,000g (vs 2500-4000g): 1.3 (0.8-2.1); for birth weight < 2,500g: 2.4 (1.2-4.8)

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Uruyama et al. (2007) ¹³	Birth registry	Cancer registry	Birth certificates	Unadjusted OR (95% CI) for birth weight (term) > 4,000g (vs 2,500-4,000g): 1.25 (0.88-1.78); for birth weight < 2,500g (term): 1.40 (0.65-3.04)
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* Cases came from two collaborative clinical trial groups

** Values calculated from the respective years of diagnosis and age at diagnosis.

*** Risk ratio was used for calculations.

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Table 2 Birth weight and risk of neuroblastoma: sensitivity analysis (random-effects model)

Study characteristic	Category	High birth weight (OR (95% CI))	Low birth weight (OR (95% CI))
Geographic area	North America	1.17 (1.0-1.38)	1.16 (0.95-1.41)
	Europe	1.21 (0.95-1.56)	1.43 (0.68-2.99)
Source of data for birth weight	Registry	1.18 (1.01-1.39)	1.11 (0.90-1.37)
	Interview	1.20 (0.93-1.53)	1.63 (1.06-2.49)
Source of case diagnosis	Registry	1.23 (1.05-1.44)	1.18 (0.87-1.60)
	Other *	1.07 (0.83-1.39)	1.36 (0.95-1.94)
Source of controls	Registry/certificate	1.20 (1.0-1.43)	1.14 (0.93-1.41)
	Other **	1.20 (0.93-1.53)	1.63 (1.06-2.49)

* included: death certificates, records, surveillance

** included: population, random digit dialing

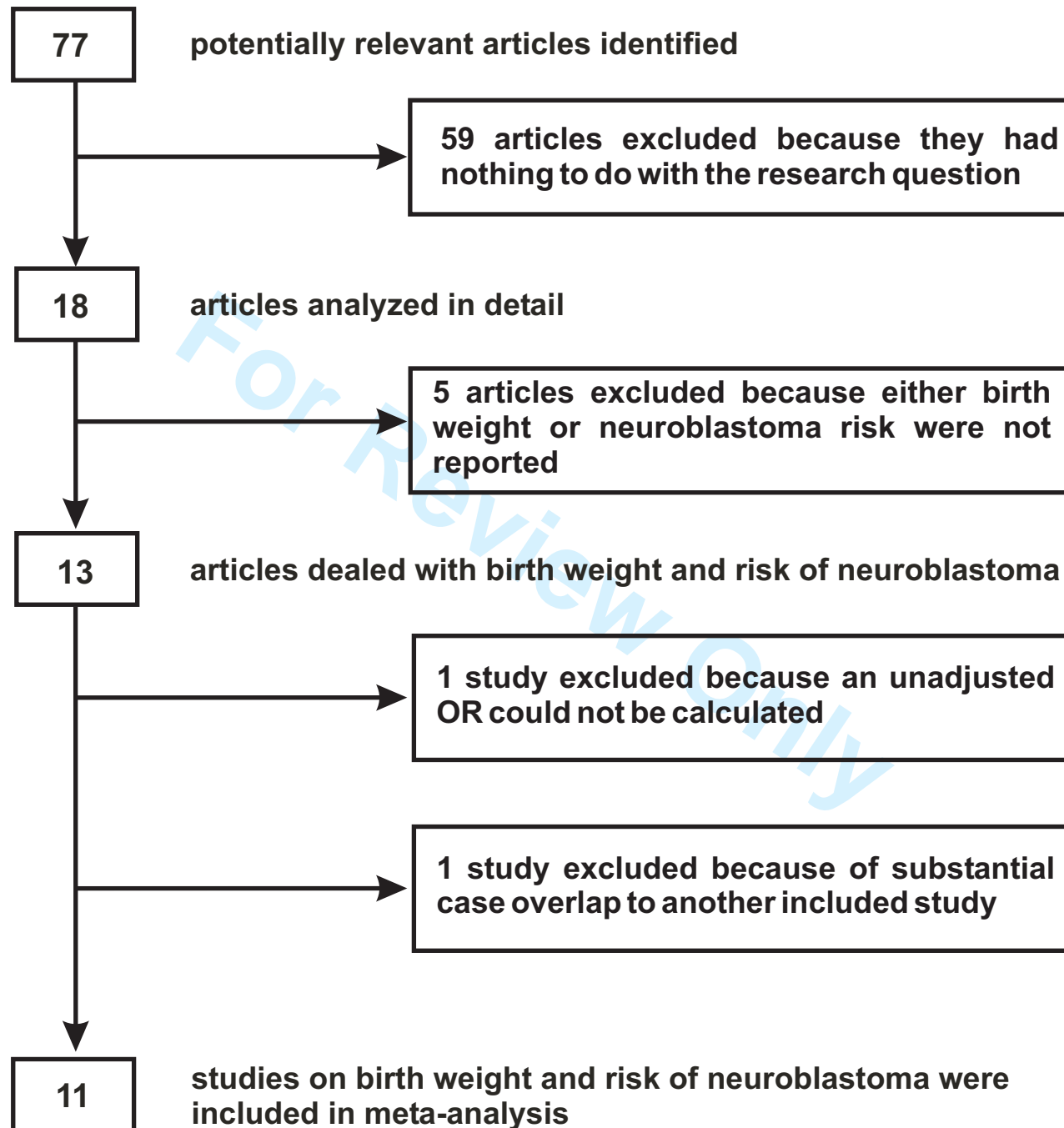
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3 **Figure legends**
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8 **Figure 1** Flow diagram of study selection process.
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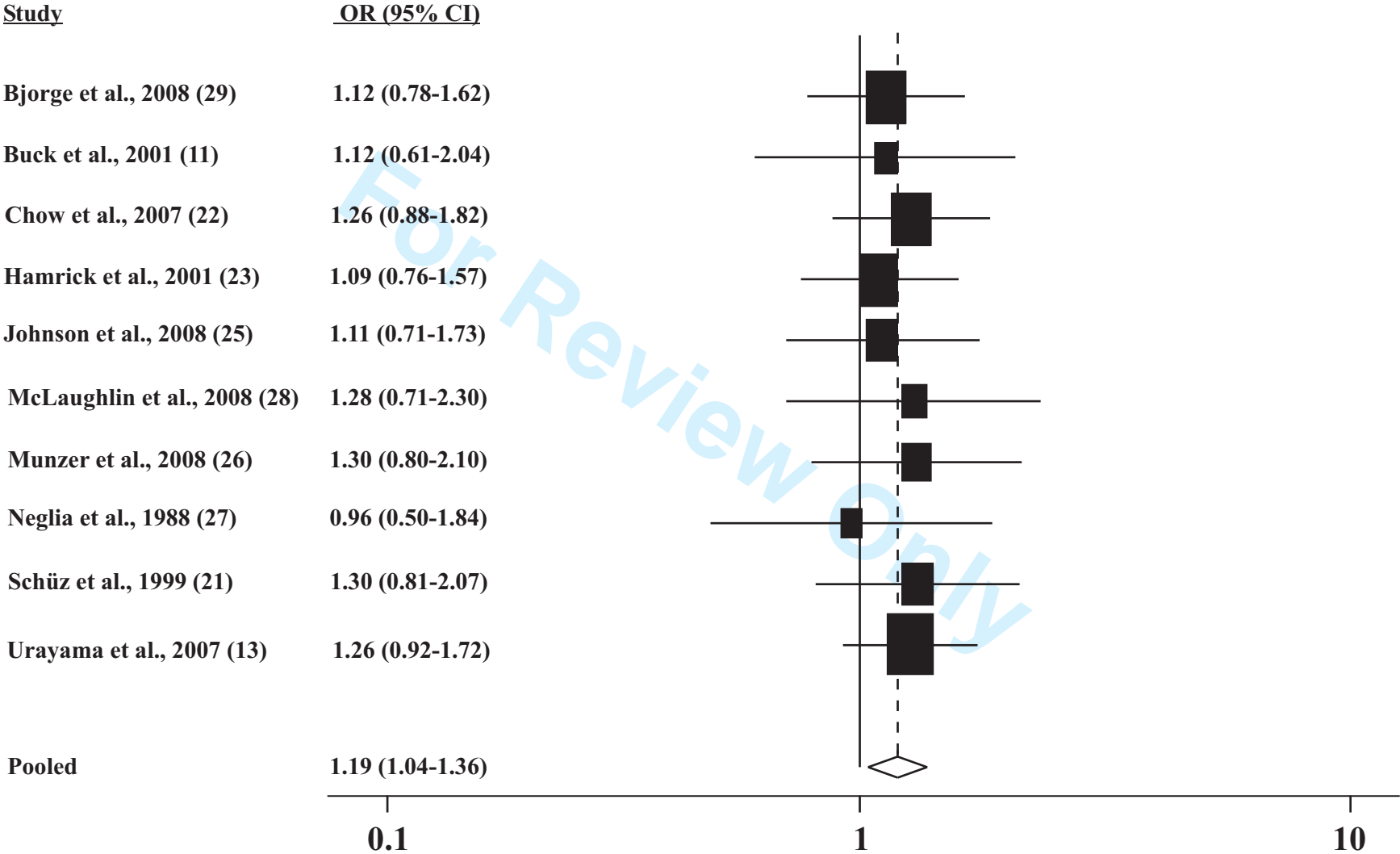
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12 **Figure 2** Odds ratios for neuroblastoma in subjects with high birth weight (>4,000 g), as
13 compared to a birth weight of <4,000 g (random-effects model).
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20 **Figure 3** Odds ratios for neuroblastoma in subjects with low birth weight (<2,500 g), as
21 compared to a birth weight of >2,500 g (random-effects model).
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High birth weight (> 4,000 g)
vs ≤ 4,000 g

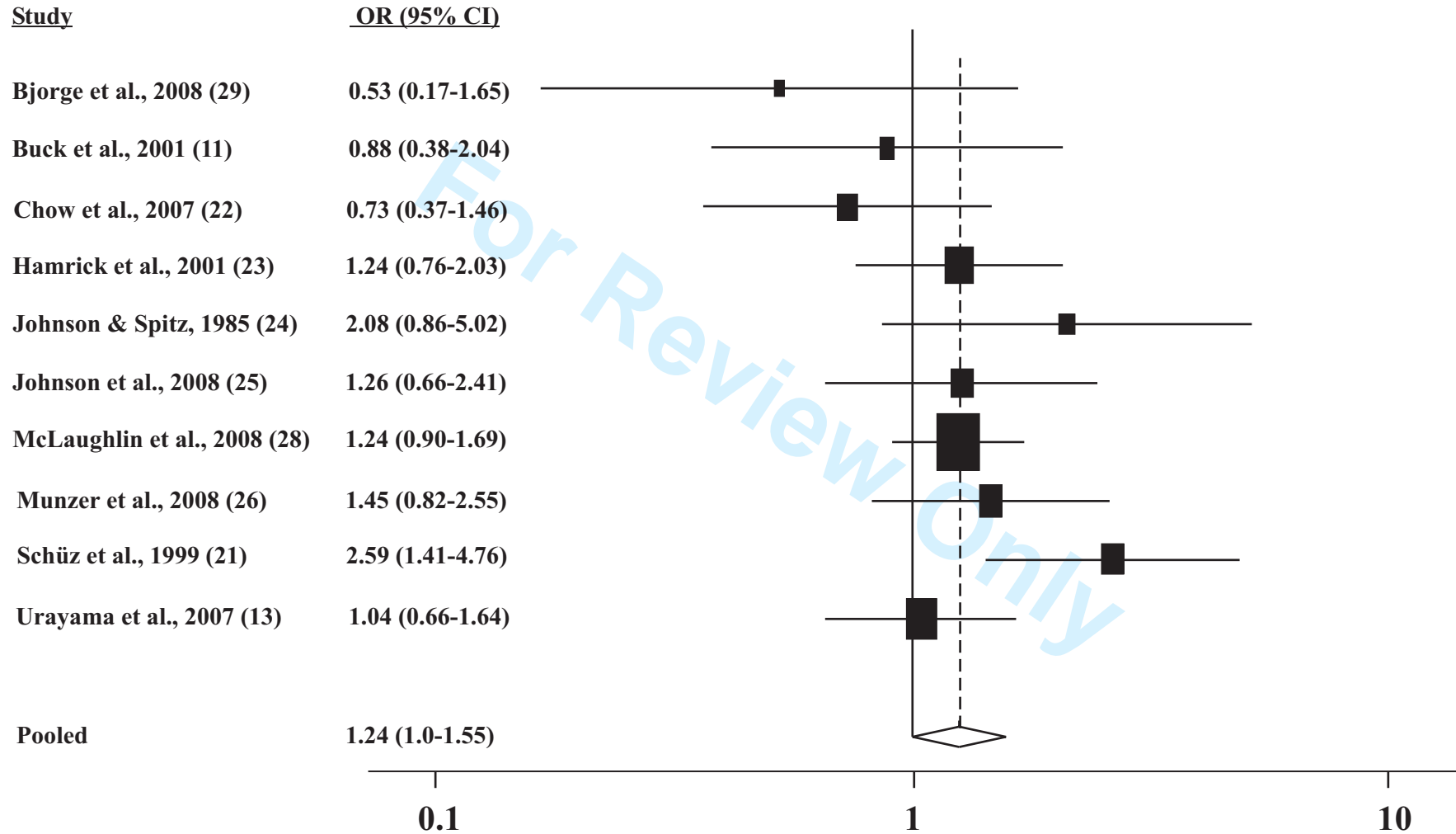


Odds ratio (95% CI) for risk of neuroblastoma

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Low birth weight (< 2,500 g)

vs $\geq 2,500$ g



Odds ratio (95% CI) for risk of neuroblastoma