INTRODUCTION

Several disorders affecting child health have their origin in the perinatal period. Perinatal factors, such as high birth weight, increase the risk of childhood overweight and adolescent obesity.\(^1,2\) Recent studies have shown that the prenatal environment has an essential impact on birth weight.\(^3\) Observational studies have found direct associations of gestational weight gain, maternal BMI at conception, and birth weight increases with birth order despite decreasing maternal pregnancy weight gain

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Abstract
Aim: We investigated whether birth order is an influencing factor for birth weight independent from maternal factors.

Methods: Data were obtained from the longitudinal cohort study LIFE Child and included 1864 children, of which 526 were only children. The 1338 siblings were ranked into first-borns (n = 570), second-borns (n = 606) and third-or-later-borns (n = 162). Children born prematurely, suffering from chronic or syndromic diseases, were excluded. We performed intra-family comparisons to reduce bias and assessed the impact of perinatal parameters, such as birth order on birth weight, using mixed models.

Results: Birth weight increased with birth order. In univariate analyses, birth order had a significant effect on birth weight-SDS with second-borns having 0.29 SDS (app. 130 g) and third-borns 0.40 SDS (app. 180 g) higher values than first-borns (\(P < .001\)). Maternal pregnancy weight gain was associated with higher birth weight-SDS (\(P < .01\)) in univariate analysis, though maternal pregnancy weight gain was lower for higher birth orders. Multivariate analyses revealed that being a second or third-or-later-born child had a stronger impact on birth weight than all maternal factors.

Conclusion: Birth order must be considered a potential risk factor for higher birth weight. Maternal pregnancy weight gain is not the driving factor for higher birth weight in siblings.

KEYWORDS
birth order, birth weight, maternal prepregnancy BMI, maternal weight gain

1 | INTRODUCTION

Several disorders affecting child health have their origin in the perinatal period. Perinatal factors, such as high birth weight, increase the risk of childhood overweight and adolescent obesity.\(^1,2\) Recent studies have shown that the prenatal environment has an essential impact on birth weight.\(^3\) Observational studies have found direct associations of gestational weight gain, maternal BMI at conception
and maternal age on birth weight. The Institute of Medicine recommends that mothers only gain a certain amount of weight depending on their prepregnancy BMI, for example, normal-weight women (BMI: 18.5-24.9 kg/m²) should gain 11.5-16 kg. Mothers who have exceeded these recommendations for maternal pregnancy weight gain have given birth to heavier children and more often had overweight adult daughters. Nevertheless, the precise factors underlying this phenomenon are not clear. Potential contributors are advancing maternal age, differences in maternal pregnancy weight gain with birth order or environmental conditions. However, previous studies have not differentiated between birth order and known risk factors for high birth weight in an intra-family setting. In sibling studies, potential risk factors for overweight, such as genetic background, socio-economic factors, migration background or nutritional habits, can be considered similar and thus less confounding. Further, previous studies have most often not excluded premature infants, had no comparison group like only children, had no data on fathers to exclude half-siblings or have only considered the effect of perinatal factors individually and not in a multifactorial model. Thus, there is still a gap of knowledge whether and which maternal and pregnancy-related factors drive this association and whether there could be birth-rank-specific dependencies.

With our data set, we were in the position to perform intra-familial comparisons and thus reduce bias by internal (genetic predisposition), external and environmental (socio-economic, nutritional, etc) influencing factors. We contribute to the current state of research by differentiating known risk factors according to birth order. Thereby, specific differences and effects of prenatal risk factors on birth weight, such as pregnancy weight gain or maternal pregnancy BMI, were compared. We aimed to investigate whether the birth order has an essential function in the development of different birth weights of siblings.

2 | PATIENTS AND METHODS

2.1 | Study population

Data were retrieved from the Leipzig Research Centre for Civilization Diseases (LIFE) Child study, an ongoing longitudinal cohort study conducted in the city of Leipzig, Germany that aims to monitor healthy child development from birth to adulthood. With recruitment age ranging between the 24th week of gestation and 18 years of age with subsequent annual follow-ups, the study combines a cross-sectional with a longitudinal design and covers a broad age range.

Participants were recruited through advertisement at different institutions such as hospitals or schools, by media or by word of mouth. Participants underwent a comprehensive assessment comprising of medical, psychological and sociodemographic assessments (clinical examinations, interviews, questionnaires). Children were free of severe diseases and medication influencing growth patterns. Written informed consent was obtained from all parents and children older than 12 years. The study and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the local Ethics committee (Reg. No. 264-10-19042010) and was registered in National Clinical Trial Register (NCT02550236).

We retrieved data of siblings having the same biological parents based on anamnestic information and of children having no siblings. Further to general exclusion criteria of LIFE Child, we excluded subjects with diabetes mellitus or who were born to mothers with gestational diabetes during one of the pregnancies (n = 18 children). We also excluded children if they were born prematurely (<37 weeks of pregnancy, n = 66 children), with unknown gestational age (n = 41 children) or were twins or triplets (n = 96 children). Half- and stepsiblings were excluded based on self-reported biological parenthood (n = 212). The remaining sample size consisted of 1864 children. We divided the participants into four groups: first-born children, second-born children, third-or-later-born children and only children (children without siblings).

Siblings were ranked by year and month of birth and by number of older and younger siblings. Birth weight and length were obtained from records of the well child surveillance examinations in Germany. Weight and length data were transformed into gender- and age-adjusted SDS values according to German newborn growth standards of Kromeyer-Hauschild. Birth weight was grouped into the three categories: large for gestational age (LGA; birth weight-SDS ≥ 1.28), appropriate for gestational age (AGA; birth weight-SDS ≥ -1.28 to 1.28) or small for gestational age (SGA; birth weight-SDS < -1.28).

Week of delivery, weight before pregnancy, weight during pregnancy at different time points and maternal height were taken from maternal medical documentation. Pregnancy weight gain was calculated as the difference of weight last recorded before delivery and before pregnancy. The last measured weight before delivery was included in calculation if measured less than 21 days before the calculated delivery date. If the weight of the mother before pregnancy was
missing in the maternal documentation, we used instead a weight of the mother, which was collected until the completed twelfth week of pregnancy to calculate the prepregnancy BMI and weight gain. Pregnancy weight gain was grouped according to recommendation of weight gain for normal-weight women into <11.5, 11.5-16 and >16 kg.3

Maternal educational level was stratified into two groups (at least a 10th grade degree equivalent to high school degree (93% of all participating mothers) vs. lower educational degree).

2.2 | Statistical analysis

All analyses were conducted using SAS Studio 3.8 (SAS Institute, Cary, NC, USA). Sample characteristics were reported as mean. Comparisons between groups were carried out using linear mixed models. All models included family identification number as a random factor, to account for the clustering of siblings. Random intercepts for subjects nested within each family were used to correct for repeated measurements per subjects respective family. Significance level was set to $P = .05$ for all analyses.

### RESULTS

3.1 | Differences in birth weight and maternal factors with birth order

The total sample consisted of 1864 children with almost equal shares of first-borns (30.6%), second-borns (32.5%) and only children (28.2%) plus a smaller proportion of third-or-later-borns (8.7%). The gender distribution, range of birth years and gestational age were comparable between groups (Table 1).

The comparison of siblings within families showed an increase in birth weight with birth order (Figure 1). Third-or-later-born children weighed on average 180 grams more at birth than first-born children. Likewise, the share of newborns large for their gestational age at birth (LGA) increased and doubled in third-or-later-born compared to first-borns. The birth length also increased with the order of birth.

Maternal factors are presented separately by birth order of the children. The maternal prepregnancy BMI increased with each further pregnancy, as expected. In contrast, maternal weight gain during pregnancy decreased with increasing birth order by almost 2 kg in later-borns compared to first-borns (Figure 1). The average

| Characteristics               | Only child | First-born | Second-born | Third-or-later-born |
|-------------------------------|------------|------------|-------------|---------------------|
| Number of participants        | 526        | 570        | 606         | 162                 |
| Gestational age (weeks)       | 39.5 ± 0.1*| 39.7 ± 0.0a| 39.6 ± 0.0b| 39.5 ± 0.1          |
| Children's parameters         |            |            |             |                     |
| Gender male (%)               | 51.5       | 51.8       | 51.8        | 53.1                |
| Birth year                    | 2006***    | 2005       | 2008***     | 2008***             |
| Birth weight (kg)             | 3.43 ± 0.02| 3.46 ± 0.02| 3.59 ± 0.02***| 3.64 ± 0.04***    |
| Birth weight group (%)        | SGA 5.35   | 5.57       | 1.67***     | 1.88*               |
|                                | AGA 83.94  | 80.61      | 77.59       | 71.88*              |
|                                | LGA 10.71  | 13.82      | 20.74***    | 26.25***            |
| Birth length (cm)             | 50.3 ± 0.1 | 50.4 ± 0.1 | 50.8 ± 0.1***| 50.8 ± 0.2**       |
| Parental parameters           |            |            |             |                     |
| Maternal age (years)          | 29.2 ± 0.2***| 28.0 ± 0.2| 31.4 ± 0.2***| 33.9 ± 0.3***      |
| Paternal age (years)          | 32.6 ± 0.3***| 30.4 ± 0.2| 33.9 ± 0.2***| 37.1 ± 0.5***      |
| Maternal prepregnancy BMI (kg/m²) | 23.3 ± 0.3*| 22.6 ± 0.2| 23.4 ± 0.2***| 23.5 ± 0.4***      |
| Maternal pregnancy weight gain (kg) | 15.9 ± 0.3 | 15.8 ± 0.2| 14.6 ± 0.3***| 14.0 ± 0.6**       |

Note: The statistical reference group were the first-born children. Results are expresses as mean ± SEM (a = 0.049, b = 0.044); means were significantly different from those for first-borns: *P < .05, **P < .01, ***P < .001.

Abbreviations: AGA, appropriate for gestational age; BMI, body mass index; LGA, large for gestational age; SGA, small for gestational age.
maternal prepregnancy BMI as well as the average weight gain during pregnancy for each of the four groups was within the recommended guidelines.

Besides maternal and paternal age being significantly higher in the only child group than for first-borns, we did not observe significant difference between first-borns and only children concerning birth weight, birth length, maternal prepregnancy BMI and pregnancy weight gain.

3.2 Association of maternal factors with birth weight

Based on the differences in prenatal and parental factors according to birth order, we tested the influence of known potential risk factors on the mean birth weight-SDS of children in univariate models (Table 2). We could show that birth order had a strong significant effect on birth weight-SDS with second-borns having 0.29 SDS and third-borns 0.40 SDS higher values than first-borns ($P < .001$). Again, only children showed no significant difference compared to first-borns regarding birth weight-SDS. Further, we found a higher maternal prepregnancy BMI, higher maternal age at the time of birth, higher maternal weight gain as well as higher gestational age to be positively associated with higher birth weight-SDS. Boys were heavier at birth than girls. The observation of birth year showed a general, slight linear increase in birth weight from 1994 to 2016. Maternal education level did not have significant impact on birth weight-SDS (Table 2).

We next applied multivariate analysis to control for all confounding factors on birth weight simultaneously (Table 3). Maternal pregnancy weight gain and maternal prepregnancy BMI showed highly significant association with birth weight with almost equal contribution according to standardised beta. This effect was independent from and in addition to the birth order that itself was the strongest factor ($P < .001$). No significant difference was found between only children and first-borns ($P = .9$). Gender and maternal age were not related to birth weight in a multivariate model.

4 DISCUSSION

Here, we showed that birth weight increases with birth order, which is not, or not entirely, attributable to increasing maternal age, BMI or pregnancy weight gain. The intra-family design allowed us to investigate prenatal risk factors independent of hereditary or environmental factors. Particularly, the third-or-later-borns had a strong increase in birth weight.

Further, we showed that an excessive maternal weight gain during pregnancy is associated with a higher birth weight-SDS of the child, supporting previous findings. It could therefore be assumed that maternal weight gain increases with the number of pregnancies. In contrast, however, we observed a significant decrease in the mother’s pregnancy weight gain with birth order. Hence, even though maternal pregnancy weight gain per se affects birth weight, it is not likely to drive the acceleration of birth weight with birth order, as it decreases with pregnancy number.

The result supports our approach of thoroughly investigating the multifactorial pathways that eventually determine birth weight through an intra-familial design. A cohort study in Japan confirmed our results by comparing the first pregnancy with the second. The authors showed a slight increase in birth weight and maternal prepregnancy BMI for the second pregnancy, while the maternal weight gain was decreased by about 100 g. In comparison, we observed a decrease of 1200 g. The same authors also demonstrated that an increase in pregnancy weight gain does not always lead to an increase in birth weight.

The dependence of birth weight on the birth order was confirmed in a multivariate model combining several covariates. We found that birth order, maternal pregnancy weight gain, gestational age and maternal prepregnancy BMI had an independent impact on birth weight, what is in line with several other studies. However, to the best of our knowledge, we were able to show for the first time that being a second or third-or-later-born child has a stronger impact on birth weight than all maternal factors.

This raises the question why the order of birth has such a strong influence on birth weight. Unfortunately, there are almost no studies that investigated the intra-family effects in detail.
Considered in our study. While we focused on maternal factors, the order on birth weight, which we have not yet or not sufficiently.

| TABLE 2 | Effects of prenatal factors by specific categories on birth weight-SDS in univariate models |
|-----------------|----------------------------------|-----------------------------|
| Risk factor      | Categories                        | Mean birth weight-SDS | P value |
| Birth order      | Only child                        | 0.16 | .3 |
|                  | First-born                        | 0.22 | reference |
|                  | Second-born                       | 0.51 | <.001*** |
|                  | Third-or-later-born               | 0.62 | <.001*** |
| Maternal prepregnancy BMI (kg/m²) | <18.5 | -0.14 | .005*** |
|                  | 18.5-25                           | 0.32 | reference |
|                  | 25-30                             | 0.44 | .1 |
|                  | ≥30                               | 0.48 | .08 |
| Maternal pregnancy weight gain (kg) | <11.5 | 0.29 | .6 |
|                  | 11.5-16                           | 0.27 | reference |
|                  | >16                               | 0.54 | <.003** |
| Maternal age (years) | <24    | 0.19 | .0496* |
|                  | 25-29                             | 0.27 | .0273* |
|                  | 30-34                             | 0.35 | reference |
|                  | 35-39                             | 0.52 | <.001*** |
|                  | 40+                               | 0.58 | .08 |
| Maternal education level | No degree-9th grade | 0.38 | .3 |
|                  | 10th+                             | 0.32 | reference |
| Paternal age (years) | <24    | 0.15 | .2 |
|                  | 25-29                             | 0.26 | .02* |
|                  | 30-34                             | 0.36 | reference |
|                  | 35-39                             | 0.36 | .5 |
|                  | 40-44                             | 0.41 | .1 |
|                  | 45+                               | 0.57 | .2 |
| Gestational age (weeks) | 37    | -0.63 | <.001*** |
|                  | 38                                | -0.18 | <.001*** |
|                  | 39                                | 0.21 | <.001*** |
|                  | 40                                | 0.51 | reference |
|                  | 41                                | 0.71 | .002** |
|                  | 42                                | 0.48 | .33 |
| Gender           | Male                              | 0.37 | <.004** |
|                  | Female                            | 0.30 | reference |
| Birth year       | 1994-1999                         | 0.25 | .01 |
|                  | 2000-2004                         | 0.31 | .04 |
|                  | 2005-2009                         | 0.34 | .3 |
|                  | 2010-2014                         | 0.35 | reference |
|                  | 2015-2016                         | 0.50 | .2 |

Note: Statistically significance of means was considered to be at *P < .05, **P < .01, ***P < .001, compared with reference category using mixed models.
Abbreviations: BMI, body mass index; SDS, standard deviation score.

We assume that other factors contributed to the effect of birth order on birth weight, which we have not yet or not sufficiently considered in our study. While we focused on maternal factors, the paternal factor exert an effect, too. We saw some increase in birth weight with increasing age of the father, as other studies have previously shown, although in our study, the effect was confined to the age range 25-29 years. Unfortunately, we could not consider paternal weight or height. A systematic review has shown that paternal height is probably associated with birth weight, while the influence of paternal BMI on birth weight was rather unclear.

Of course, the social environment is also highly likely to play a role. Nevertheless, with our intra-familial setting those factors can be considered relatively constant between siblings. Brenøe and Molitor found that socio-economic characteristics (stress, parental wage), behavioural aspects (smoking, check-ups) or hospitalisation rates for pregnancy complications did not explain the positive relation between birth order and health.

Hence, the biological intrauterine component is likely to change maternal physiology in favour of later-borns and needs to be further investigated with regard to sibling pregnancies. Differences in the rate of foetal weight gain throughout pregnancy, the overall quality of life of the mother during pregnancy, maternal dietary modifications.

A study by Silvestrin examined secular trends in birth weight from 1996 to 2013 through maternal education, one of the most important determinants of socio-economic status. In children born to mothers with lower education, birth weight increased slightly, while it decreased in those born to mothers that are more educated. Participants in our study had birth years between 1994 and 2016, and the range in birth years (spanning 20 years) matched closely between the birth order groups. The mean birth year of 2nd and 3rd-borns was 2008, which is approximately 3 years later than

| TABLE 3 | Effects of risk factors by specific categories on birth weight-SDS in multivariate models |
|-----------------|----------------------------------|-----------------------------|
| Risk factor      | Estimate (Standardised Beta Coefficient) | P Value |
| Birth order      | Only child                        | -.01 | .9 |
|                  | Second-born                       | .24 | <.001*** |
|                  | Third-or-later-born               | .35 | .004** |
|                  | First-born                        | 0 | reference |
| Maternal prepregnancy BMI | .17 | <.001*** |
| Maternal age     | .02 | .5 |
| Gestational age  | .27 | <.001*** |
| Gender           | -.03 | .4 |

Note: Means were significant at: ** P < .01, *** P < .001. Abbreviation: BMI, body mass index.

We assume that other factors contributed to the effect of birth order on birth weight, which we have not yet or not sufficiently considered in our study. While we focused on maternal factors, the
that of first-borns, but this reflects the advancing maternal age (3-5 years older). Although we have seen a slight increase in birth weight (by about 140 g) over the 20-year observational period, the birth weight increase of later-borns compared to first-borns with a 3-year age difference is not likely due to a secular trend. Further, we have also examined whether maternal education has an influence on birth weight. We divided the mothers into two groups (at least a 10th grade degree equivalent to high school degree vs. lower educational degree). However, Silvestrin had made a division into less than 8 years and more than 12 years of education. While Silvestrin found differences between the two educational groups on birth weight, our data showed no significant effect. The small number of mothers in the lower educational level may have biased our result, since 93% of all participating mothers had at least a 10th grade degree.

Birth weight is known to be associated with (childhood) obesity risk. Nevertheless, Thoren et al.\(^2\) showed that this association of birth weight with obesity was not retained in 16- to 18-year olds. However, in their study, among other things, weight gain from birth to one year of age was associated with obesity at the age of 16-18 years. This corresponded, according to a study by Budree,\(^3\) to the age at which birth weight was an important predictor of weight gain, regardless of ethnicity or socio-economic outcome. We have previously shown that a critical phase for developing overweight is at the age of 2-6 years.\(^4\) Children who were obese at this time will mostly be obese as adults. Further, children born with a high birth-weight (large for gestational age) had a 1.55 times higher risk of adolescent obesity.

While the large sample size is a strength of our study, there are some limitations. As with many cohort studies relying on voluntary active participation, our cohort is biased towards higher socio-economic status (SES) than the representative population. Consequently, our study did not include data from rural areas. Nevertheless, as we performed intra-familial analyses, we consider the confounders to affect all siblings in a similar way.

We have to acknowledge that the classification into half-/stepsiblings or biological siblings having the same mother and father relies on the correctness of the parents’ statements.

There are several possible aspects that affect the birth weight, which had not been taken into account, for example, the food intake or smoking during pregnancy. However, we excluded mothers with gestational diabetes because it has been further shown to be associated with higher birth weights.\(^5\)

Despite these limitations, our study differs from most previous work. A main key strength is the intra-familial comparisons of siblings in a large sample size and a differentiating of known risk factors of birth weight according to birth order. Further, this study covers participants born between 1994 and 2016. Yet, our data also reflect results for current birth years. By using SDS values, we were able to compare birth weight regardless of gender.

In conclusion, our results demonstrate a strong positive association between increasing birth order and birth weight and this association was independent from known perinatal risk factors such as maternal weight gain during pregnancy, whereas maternal age or maternal prepregnancy BMI overall showed an influence on birth weight.

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**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

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