

ORIGINAL ARTICLE

Observational study on the neonatal outcome during the COVID-19 pandemic in Germany

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Abstract

Aim: We aimed to determine stillbirth, preterm birth, perinatal complications, and the developmental outcome of children born preterm during the COVID-19 pandemic in Germany.

Methods: National data from the perinatal survey of preterm and term infants born in 2017–2020 between 22 March and 31 December were evaluated. Neurodevelopment of preterm infants at 2 years corrected age was tested with the Parent Report of Children's Abilities-Revised questionnaire and by clinical testing with Bayley scales, either before or during the COVID-19 pandemic. Statistical significance was calculated using a Pearson's chi-square-independence test and a linear regression model.

Results: In 2020, there was an increase of stillbirths of 0.02% ($p=0.01$) and a decrease in preterm births by 0.38% ($p<0.001$). No changes were found in a representative subgroup of infants with regard to neurodevelopmental scores (mental developmental index and psychomotor developmental index) or in parent survey data (non-verbal cognition scale and language development scale).

Conclusion: Increasing rates of stillbirths and decreasing preterm births in Germany were observed. Existing networks might stabilise neurodevelopment of preterm infants during the COVID-19 pandemic.

KEYWORDS

COVID-19 pandemic, neurodevelopment, perinatal outcome, preterm infants, stillbirth

1 | INTRODUCTION

The COVID-19 pandemic had far reaching indirect effects on the health of preterm and new-born infants, even if pregnant women and preterm infants were rarely affected by a severe course of COVID-19.¹ However, there were clear differences between nations. According to Chmielewska et al.² an increase in preterm birth and

stillbirth rates has been reported, especially in countries with a low average income. Countries with a high average income, on the other hand, reported a significant decrease in preterm births as well as no difference. To date, objective publications on neonatal outcomes during the COVID-19 pandemic in Germany are not available.

In addition, lockdown measures could have had a negative impact on the development of preterm infants by restricting support

Abbreviations: GNN, German Neonatal Network; IQR, interquartile range; IQTIG, Institute of Quality Assurance and Transparency in Health Care; MDI, mental developmental index; PARCA-R, Parent Report of Children's Abilities-Revised; PDI, psychomotor developmental index.

M. Lau and V. Kraus have contributed equally to this work.

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for them and their families after discharge from the hospital. As part of the present project, the motor and verbal abilities of children born preterm were evaluated with a parent survey, and clinically the cognitive and the psychomotor development with Bayley scales at corrected age of about 2 years.

The aim of our study was to obtain objective data on stillbirth, preterm birth, and the motor and neurocognitive development of preterm infants aged 2 years under COVID-19 pandemic conditions.

2 | PATIENTS AND METHODS

We obtained the data on preterm and new-born infants in Germany before and during the COVID-19 pandemic, including birth and perinatal data from the Institute of Quality Assurance and Transparency in Health Care (IQTIG). In addition, we collected data concerning the neurocognitive development of very small preterm infants at the age of 2 years. The German Neonatal Network (GNN) cohort was evaluated by the Parent Report of Children's Abilities-Revised (PARCA-R) and the Munich cohort by clinical examination using Bayley II and III.

2.1 | IQTIG data

National secondary data on all births registered in Germany were obtained from the IQTIG. These data were used to evaluate the periods of the first lockdown phase of the pandemic between 22 March and 31 December 2020, in comparison to the average of the previous 3 years 2017–2019 in order to minimise opposing changes. Accordingly, the data from children born between 1 January and 21 March in 2017–2020, respectively, are not being taken into consideration. When comparing the present data analysis with the annual evaluations of the Federal Statistical Office in Germany,³ it should be noted that the discrepancy in absolute numbers follows the selection of the period. In the following section, only the year is given in reference to the periods.

Preterm infants were defined as born before 37 and term infants with a gestational age ≥ 37 weeks. Furthermore, there was a split between extremely and very low birth weight infants <1500g and low birth weight infants >1500g. To compare the years 2017, 2018, and 2019 with the year 2020, the mean value of these 3 years was used for testing and was explicitly stated in order to get a representative year.

In all live births, the comparisons were performed between preterm and term born infants using the IQTIG data. We analysed quality indicators including the rate of asphyxia, maternal deaths, emergency Caesarean sections, out of hospital births, and admittance to the hospital within the first 7 days of life (Table 1). These data were analysed descriptively. The indication of counts of the years 2017–2019 were divided by 3 to get the average. The number of stillbirths and preterm births from the national perinatal data from the IQTIG was analysed using Pearson's chi-square-independence test. The level of the tests was set at 0.05.

Key Notes

- During the COVID-19 pandemic in Germany, we observed increased stillbirths and decreased preterm births, but no difference concerning asphyxia or neurodevelopment of preterm infants at the age of 2 years.
- Guidance of pregnant women is needed to ensure timely admission to medical systems.
- Reliable networks exist to support neurodevelopment of preterm infants also under pandemic conditions.

2.2 | PARCA-R data

To analyse the neurocognitive and motor outcome of preterm infants at the corrected age of 2 years, the PARCA-R questionnaire^{4–6} was used in the GNN cohort.

The PARCA-R was sent to parents whose participating child was at a corrected age of 2 years. From the parental information, the non-verbal cognition scale and the language development scale were calculated. The participating children were divided into two comparison groups during and after the spring lockdown. The spring lockdown was defined as January to April 2021 and the period after as July to October 2021. The time periods were chosen as described above because of the project duration. The German version of the PARCA-R is only validated for children with German as their native language, which is the reason why the analysis was adjusted for the mother's origin. Based on the validation data of the University of Leicester,⁴ we adjusted the raw scores accordingly for gender, gestational age, and the age upon completion of the questionnaire. Two multiple linear regressions were used for evaluating the impact of the timepoint of filling out the questionnaire during or after spring lockdown on non-verbal cognition scale and language development scale. Adjustments were made for intraventricular haemorrhage grade III or IV, German origin of the mother, and previous or multiple births.

2.3 | Munich cohort

The clinical evaluation of the neurocognitive and motor development was performed with the Bayley Scales of Infant Development test II and III. The children were born between January 2016 and April 2020 in the neonatology department of Munich Municipal Hospital. Results of Bayley III score values correlate with those of PARCA-R-surveys.⁵ No tests were performed between March 3 and April 20 2020 due to complete lockdown. The infants were divided into three partly overlapping groups. Children born before COVID-19 in 2016–2017 were allocated to phase -1, children born during COVID-19 in 2018–2020 were allocated to phases 0 to 3, and children born during COVID-19 in 2019–2020 were allocated to phase 4. We compared children born pre COVID-19 in phase

	2017–2019 (n = 1 815 118)		2020 (n = 594 728)		p-value
	Absolute number	Percentage	Absolute number	Percentage	
Live birth	1 808 414	99.63	592 392	99.94	
Stillbirth	6 704	0.37	2 336	0.39	0.0103 ^b
Neonates and preterm infants admitted to hospital within first 7 days of life	238 654	13.20	77 646	13.11	
Preterm infants admitted to hospital within first 7 days of life ^a in total	103 429	43.34	30 706	41.00	<0.001 ^b
Gestational weeks 33–36	74 518	72.05	22 744	74.07	
Gestational weeks 32–27	23 765	22.98	7 152	23.29	
Gestational weeks 24–26	3 975	3.84	1 223	3.98	
Gestational weeks 22–23	1 171	1.13	346	1.13	
Asphyxia					
Without hypothermia	5 408	0.30	1 759	0.30	
With hypothermia	1 950	0.11	651	0.11	
Emergency Caesarean sections					
Preterm infants	5 704	24.44	1 909	24.24	
Term infants	17 830	75.76	5 903	75.56	
In- and out born rates					
In-hospital birth	1 773 690	98.08	589 292	99.47	
Out-of-hospital birth	2 481	0.14	855	0.14	

^aPercentages based on total number of neonates and preterm infants admitted to hospital within first 7 days of life.

^bPearson's chi-square-independence test was used to derive the p-value.

-1 with children born during COVID-19 in phase 4. The group phase 4 had the longest duration of COVID-19-related restrictions during neurocognitive development. Scale values of Bayley II and III differ in total scores tested in children at 18–22 months corrected age.⁷ In the study comparing Bayley II and III values in a randomised controlled trial, children reached higher scores in Bayley III than in Bayley II testing. The mean difference for mental developmental index (MDI) was calculated with $+14.1 \pm 12.9$ points, and the mean difference for psychomotor developmental index (PDI) was calculated with $+9.0 \pm 11.9$ points on the scale. We therefore adjusted the MDI and PDI scores of Bayley II testing accordingly.⁷

Two multiple linear regressions were conducted to evaluate the effect of testing time points pre COVID-19 of children born in 2016–2017 versus COVID-19 phase 4 (children born in 2019–2020) on MDI and PDI scores. The models were adjusted for gestational age, female gender, corrected testing age, intraventricular haemorrhage grade III or IV, and German origin.

The Bonferroni-adjusted type I error was accordingly set at 0.0125 for four tests for the testing of motor and neurocognitive development of preterm infants aged 2 years in the PARCA-R data and the Munich cohort for an overall significance level of 0.05.

TABLE 1 Live birth, stillbirth, and population-based numbers of perinatal complications. Percentages of perinatal complications on live births, unless described differently. Preterm defined as <37 weeks of gestation. p-values only mentioned when derived.

The statistic program R 4.2.1 (The R Foundation) was used for evaluation and graphic representation of the IQTIG data. Analyses of the Bayley data were performed with IBM SPSS Statistics Version 28.0.1.1 (IBM).

3 | RESULTS

3.1 | IQTIG data results

We compared the total births registered in 2020 and in the previous 3 years from 2017 to 2019. A total of 592 392 births were registered in 2020, and an average of 602 805 per year was registered in 2017–2019. In 2020, we found 2 336 stillbirths. The difference was significant compared to that in the previous 3 years ($p = 0.0103$) (Table 1). In the registered period in 2020, significantly fewer preterm infants were born ($p < 0.001$) (Table 1). Splitting up the number of preterm births per year, there is a trend towards a decrease in preterm births over the period from 2018 to 2020.

There was no difference in the rate of asphyxia (0.30%) with and without therapeutic hypothermia (Table 1). About 0.07% of children per year, who were admitted to the hospital within the first 7 days

of life, died (Table 1). There was no relevant difference in maternal deaths related to birth, emergency Caesarean sections, and out-versus in-born hospital deliveries (Table 1).

3.2 | PARCA-R data

A total of 961 PARCA-R questionnaires were sent out to the families. Return rate was 37.4%. Of those, 202 questionnaires (56.27%) could be included in the analysis, with 43 children reaching 2 years during the spring lockdown and 159 children reaching 2 years after the spring lockdown.

There were no apparent differences, neither in the non-verbal cognition scale in median interquartile range (IQR) nor in the language development scale (Figure S1). Girls performed worse on the language development score than boys (Figure S1).

After adjustment for potential influencing variables in a multiple linear regression, there were still no significant differences between the groups ($p=0.907$ for non-verbal cognition and $p=0.178$ for language development) (Table S1).

3.3 | Results of the Bayley scales of infant development

The clinical Bayley cohort included 89 children with a median gestational age of 29.9 weeks (IQR 27.0–31.4 weeks). The children were tested at a median corrected age of 23.00 months (IQR 22.1–23.3 months). The clinical characteristics of the cohort are presented in Table S2. Patients with non-German origin were more frequent in 2016–2017. We found no apparent differences with regard to Bayley MDI and PDI between children tested before COVID-19 and during the COVID-19 pandemic (Figure S2). The multiple linear regression model adjusted for gestational age and other variables did not alter these results ($p=0.312$ for MD, $p=0.234$ for PDI) (Table S3).

4 | DISCUSSION

This study describes the short- and long-term outcome of preterm and new-born infants in Germany during the COVID-19 pandemic. We found a slight but significant increase of stillbirths in 2020 compared to 2017–2019. The decline in preterm births observed in Germany in 2020 followed the trend of the previous 3 years.³ The decrease was largest in the group of the late preterm between 32 and 36 weeks of gestation. Staying at home, increased general hygiene, less social contact, and presumably less physical activity had a protective effect on the pregnancy.⁸ These pandemic-related changes could have led to more early-term infants rather than late-preterm infants. During the lockdown, prenatal check-ups were significantly reduced in many places, including Germany.⁹ In addition, pregnant women may have been afraid of contracting COVID-19 in the hospital or may have been suffering from supply gaps.^{10–12}

Therefore, it could be speculated that the decrease of preterm infants could also be linked to the increase of stillbirths as a result of delayed obstetric presentation.^{9,13–15}

Within Europe, the perinatal outcome during the pandemic varied greatly. Studies from Austria or Italy, consistent with the data presented here, showed a decrease in preterm births, but an increase in the stillbirth rate during the lockdown.¹⁶ An almost threefold increase in the stillbirth rate during the first, very strict lockdown has been reported in Italy in particular. Accordingly, the severity of the lockdown seemed to correlate with hesitancy or avoidance in visiting the hospital, and maybe with the severity of perinatal complications.¹⁷ Denmark, on the other hand, reported a reduced number of preterm infants^{18,19} without an increase in the stillbirth rate.²⁰ Data from the Netherlands, England, and Australia mainly pointed to a lower rate of induced preterm birth^{18,21,22} while the rate of spontaneous preterm births remained unchanged. The authors attributed the reduced rate of premature births to a lower level of maternal stress during the lockdown.¹⁹ This is contradicted by publications that described the significantly poorer mental health of pregnant women as compared to before the pandemic.^{23,24} The perinatal data did not suggest any relevant increase or decrease in asphyxia. The number of births related maternal deaths according to our data were similar compared to the pre-pandemic period, but was not formally tested. Out-of-hospital births neither increased nor decreased during the lockdown. The trend towards home births presented in the literature^{25,26} therefore could not be confirmed. The evaluation of the motor-cognitive and language development scores of the PARCA-R did not show any differences between spring lockdown and post-lockdown. The interpretation is impaired by the limited number of evaluable questionnaires, especially of those from the lockdown period. The lack of differences between the investigation period and the comparison period could be explained not only by the limited number of cases but also by the fact that the pandemic was still ongoing. Gaps in care may not have been closed yet and the children had not yet made up for possible development deficits. On the other hand, the lockdown may also have had a positive impact on the development of the very small preterm infants because parents worked from home and siblings were cared for at home, which may have resulted in more family input. According to literature, the mere fact that a child was born during the pandemic seemed to have a negative impact on neurocognitive development compared to the years before,²⁷ although critical voices have also been raised towards this theory.²⁸ Based on their validation data, the PARCA-R authors assumed that girls would perform better in the language development score and adjusted the score accordingly. This means that a girl with the same raw score as a boy of the same age received a lower score. Our evaluations showed, however, that girls performed worse on the language development score. This may be due to the fact that, on average, the girls in our cohort had a slightly lower gestational age than the boys. This might explain a lower raw score, and our results may therefore be an overcorrection of the language development score. To reduce the above-mentioned limitations, we analysed clinical Bayley neurodevelopmental score data from one

neonatal centre in Munich. Bayley neurodevelopmental scores type III correlate with PARCA-R questionnaires.⁵ We furthermore extended the study groups and periods to compare children without and with the longest possible influence of the COVID-19 pandemic restrictions. We found tendencies to score lower in cognitive and motor development at corrected age of 22.16–22.15 months with Bayley III scores in children born in 2018–2020 compared to children born before the pandemic in 2016 and 2017.

4.1 | Strengths and limitations

The strength of our study are the population-based data assessed by the German national neonatal and perinatal data collection for evaluation of the short-term outcome. These registry data are complemented by two methods for assessment of the long-term outcome in representative subgroups including PARCA-R questionnaires and clinical Bayley III examination. This data collection in 2020 during the COVID-19 pandemic makes slight but significant changes in stillbirths, which is the most severe perinatal complication, visible. Although we did not find a trend in the stillbirth rate even in extending the historical cohort to the previous 3 years in contrast to other outcome parameters, these data are observational data only and do not allow to derive a causal relationship with the COVID-19 pandemic.

Further limitations of our study consist of the relatively small sample size of the PARCA-R survey and the Bayley follow-up group compared to the German registry data. Moreover, the Bayley exam was conducted in one single centre of the GNN, possibly resulting in a referral bias. Different versions of the Bayley test were used, and results therefore had to be adjusted to the version for comparison. The timely limited observation periods only at the beginning of the pandemic with a retrospectively relatively short period of restrictions could have influenced possible effects in the short- as well as the long-term outcome. Another possible referral bias in the clinical examination group is the need for presentation in a hospital, as therapies and medical contacts were reduced during the lockdown. It is possible that the risk population of preterm infants was not able or did not want to come to the follow-up examinations, even outside of the complete lockdown period. So, severe neurocognitive and motor developmental sequelae could have been missed or be manifested yet.

5 | CONCLUSION

We observed a slight but significant increase in stillbirths during the COVID-19 pandemic. Although a causal relationship cannot be derived, we are concerned about this serious complication which might be a result of reduced prenatal care. Nevertheless, based on the data presented, the concerns about profound negative short- and long-term effects of COVID-19 pandemic-related restrictions could not be confirmed in our patient cohorts. We propose to be diligent in prenatal education of the families to visit check-ups and recognise

warning signals for imminent emergencies. Concerning postnatal care especially in the vulnerable group of the preterm infants, we emphasise that supportive therapies and networks for the very small preterm infants should be preserved and also strengthened in the future.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data from quality assurance procedures according to § 136 SGB V of the Federal Joint Committee were used.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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