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Original research article

Incidence of congenital microcephaly in the Czech Republic: The effect of maternal age

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Abstract
Objective: Congenital microcephaly is a diverse group of congenital anomalies characterized by a significantly reduced head circumference at birth. The incidence varies widely across regions. This study focuses on the incidence of microcephaly in the Czech Republic.
Methods: A retrospective analysis was conducted using data from the National Registry of Congenital Anomalies of the Czech Republic. All cases coded as microcephaly (Q02 code in the 10th revision of the International Classification of Diseases) between 2000 and 2020 were included.
Results: A total of 274 cases of congenital microcephaly were identified, with an incidence rate of 1.22 per 10,000 births. The sex ratio was significantly skewed toward females (0.63:0.37). Microcephaly was significantly more frequent among mothers aged less than 25 years (1.68 per 10,000) and over 35 years (1.51 per 10,000), compared to those aged 25–34 years (1.03 per 10,000).
Conclusion: This research provides the most detailed population-based estimate of congenital microcephaly in the Czech Republic. The study reports a lower relative incidence compared to many other countries. The findings highlight significant associations with maternal age and a notable female predominance, warranting further investigation into genetic and biological mechanisms.

Keywords: Congenital anomalies; Czech Republic; Incidence; Maternal age; Microcephaly

Highlights:
- The population incidence of congenital microcephaly in the Czech Republic is 1.22 per 10,000 births. • Congenital microcephaly was significantly more frequent in females. • Incidence varies by maternal age and is higher in the youngest and oldest mothers.

Introduction

Congenital microcephaly is a broad term referring to a heterogeneous group of congenital anomalies characterized by a significantly reduced head circumference at birth. It is traditionally classified into primary (congenital) microcephaly, which results from genetic or developmental factors affecting brain growth *in utero*, and secondary (acquired) microcephaly, which occurs due to postnatal brain insults. This classification primarily focuses on timing rather than the underlying etiology (Asif et al., 2023; DeSilva et al., 2017; von der Hagen et al., 2014).

The reported incidence of congenital microcephaly varies significantly across countries and surveillance systems. A study from the EUROCAT network estimated an overall incidence of 1.53 per 10,000 live births, with regional variations ranging from 0.4 to 4.3 per 10,000 births (Morris et al., 2016). Such discrepancies largely stem from differences in definitions and diagnostic criteria used across registries. Some surveillance systems define microcephaly using a threshold of <2 standard deviations (SD) below the mean head circumference, while others apply a stricter cutoff of <3 SD (Asif et al., 2023; Dolk, 1991; Morris et al., 2016). The Czech Republic follows a percentile-based approach, defining microcephaly as a head circumference below the 3rd percentile for gestational age and sex.

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The causes of microcephaly include a variety of genetic and non-genetic factors. Major genetic causes include chromosomal abnormalities, such as the main autosomal trisomies (Trisomy 13, 18, and 21 syndromes) and numerous microdeletion syndromes (such as Cri du Chat syndrome, Wolf–Hirschhorn syndrome, Miller–Dieker syndrome, and many others) (Abuelo, 2007). As of May 2025, the OMIM database (www.omim.org) lists 30 genes (MCPH1-30) associated with primary (mostly isolated) microcephaly. Furthermore, microcephaly can be part of a complex phenotype in various monogenic malformation syndromes, including Cornelia de Lange syndrome, Smith–Lemli–Opitz syndrome, and Nijmegen breakage syndrome (Abuelo, 2007; DeSilva et al., 2017). Genetic laboratory testing using massive parallel sequencing is recommended for detailed molecular diagnostics, especially for primary microcephaly cases (Wang et al., 2023).

The non-genetic factors include various types of teratogens. The Zika virus outbreak in Brazil during 2015–2016 brought significant attention to viral infection-associated cases of congenital microcephaly, which may also be caused by prenatal infections from other viruses, namely those in the TORCH group (rubella virus, herpes simplex virus, and cytomegalovirus). Congenital anomalies of the brain – including microcephaly – can also be caused by prenatal infections with *Toxoplasma gondii* (Ashwal et al., 2009; Chien and Chen, 2024). Microcephaly can also be caused by radiation exposure, maternal phenylketonuria, or excessive alcohol consumption during pregnancy (as part of fetal alcohol syndrome), among many other conditions (Abuelo, 2007; Chien and Chen, 2024).

Despite extensive international data, population-based estimates for microcephaly in the Czech Republic remain limited. This study aims to provide a detailed epidemiological analysis of congenital microcephaly in the Czech Republic using population-wide national health registry data spanning 21 years (2000–2020).

Materials and methods

We performed a retrospective epidemiological study using population data from the official health registries of the Czech Republic. The National Registry of Reproductive Health is managed by the Institute of Health Information and Statistics of the Czech Republic. For our study, we used data from two sub-registries: the National Registry of Congenital Anomalies and the National Registry of Newborns. The registration process is population-wide, compulsory by national law, and does not require informed consent (Šípek et al., 2014).

The study database of congenital microcephaly cases was compiled from the above-mentioned registries. All cases with the corresponding ICD-10 code (Q02) in births were included. In the Czech Republic, the threshold between normal and abnormally small head circumference is the 3rd percentile. There are no specific inclusion criteria regarding associated anomalies (all relevant ICD-10 codes are reported for each affected individual, including syndromic codes) or clinical symptoms (cases with and without neurological deficits are reported).

The study period spans 2000–2020 (21 years). The following variables were obtained for each case: sex, maternal age, pregnancy multiplicity, and associated diagnoses (other than Q02).

Incidence rates and comparisons are based on the aforementioned registries of all children born during the study period (2000–2020). However, the distributions of sex, maternal age, and pregnancy multiplicity in the Q02 group were compared with a control group defined as all children born during the study period without any diagnosis of congenital anomaly (ICD-10 codes Q00–Q99).

Statistical analysis was performed using Stata software, version 15 (StataCorp LLC, College Station, Texas, U.S.A.). Fisher's exact test was used for comparisons of incidence rates and diagnostic groups (microcephaly vs. anomaly-free) in terms of sex ratio, maternal age categories, and pregnancy multiplicity.

For a detailed comparison of maternal age distributions in the microcephaly and control groups, the Kolmogorov–Smirnov test was used. Mean maternal age between the two groups was compared using the Welch's unequal variances *t*-test. Statistical significance was set at $p < 0.05$.

Results

During the study period, 274 children (271 live births and 3 stillbirths) were born with microcephaly in the Czech Republic (1.22 per 10,000 births in relative numbers) – the details are summarized in Table 1. In 144 cases (52.6%), the microcephaly was isolated (Q02 was the only congenital anomaly code noted for that particular case). In 14 cases (5.1%), microcephaly was associated with chromosomal abnormalities (ICD-10 codes Q90–Q99), and in 116 cases (42.3%), microcephaly was associated with another congenital anomaly (ICD-10 codes Q00–Q01, Q03–Q89) – see Table 1.

Out of all cases, 171 were females and 101 were males (in two cases, the sex was not determined), with a female-to-male sex ratio of 0.63:0.37. In the control group of 2,151,570 children, the female-to-male ratio was 0.49:0.51. The higher proportion of females in the microcephaly group is statistically significant ($p < 0.001$).

Regarding maternal age, we found the average age of mothers of children with microcephaly to be approximately 0.6 years younger than that of mothers in the control group (28.5 years vs. 29.1 years, respectively). However, this difference was not statistically significant. The overall distribution of maternal age was further analyzed using the Kolmogorov–Smirnov test, which found a statistically significant difference ($p = 0.001$). As shown in Fig. 1, this difference is primarily due to the greater proportion of young mothers in the microcephaly group compared to the control group. The greatest vertical distance between the two curves is related to the proportions of maternal age up to 26 years, namely 42.0% in the microcephaly group, and 30.1% in the control group (a difference of 11.9 percentage points).

Another, though less pronounced, difference was observed for mothers aged 35 years and older, where the proportion in the microcephaly group was slightly greater than in the control group. In terms of commonly used maternal age categories (≤24 years, 25–34 years, and ≥35 years), the proportions in the microcephaly group were 25.2%, 56.2%, and 18.6%, respectively, which differed significantly ($p = 0.001$) from the control group proportions of 18.3%, 66.7%, and 15.0%, respectively.

Incidence rates of microcephaly were highest in the youngest maternal age group (1.68 per 10,000 live births) and in the oldest maternal age group (1.51 per 10,000 live births), both of which were statistically significantly higher than in the middle maternal age group (1.03 per 10,000 live births). Comparison with the youngest group yielded $p = 0.001$, while comparison against the oldest group gave $p = 0.024$.

Table 1. Incidence of congenital microcephaly in the Czech Republic

Year	Total cases	Relative incidence	Isolated cases	Associated with chromosomal anomalies	Associated with other congenital anomalies
2000	14	1.54	7	3	4
2001	13	1.43	8	1	4
2002	16	1.72	10	2	4
2003	14	1.49	7	1	6
2004	12	1.23	5	1	6
2005	9	0.88	4	0	5
2006	7	0.66	6	0	1
2007	10	0.87	6	0	4
2008	14	1.17	5	0	9
2009	13	1.10	3	1	9
2010	17	1.45	5	1	11
2011	17	1.56	10	0	7
2012	11	1.01	5	1	5
2013	9	0.84	6	1	2
2014	8	0.73	4	1	3
2015	9	0.81	4	1	4
2016	9	0.80	6	0	3
2017	16	1.40	6	0	10
2018	12	1.05	6	0	6
2019	19	1.69	15	0	4
2020	25	2.27	16	0	9
Total	274	1.22	144	14	116

Note: Relative numbers are calculated per 10,000 live births. Chromosomal anomalies are defined as diagnoses with Q90–Q99 ICD-10 code. Other congenital anomalies are defined as diagnoses with ICD-10 codes Q00–Q01, Q03–Q89.

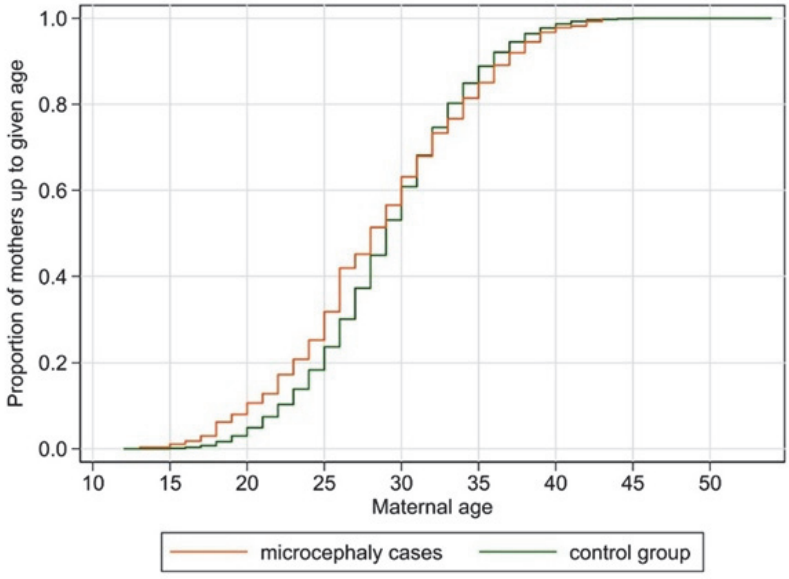

Fig. 1. Distribution of maternal age in microcephaly cases and control group

We also analyzed the incidence of microcephaly in singletons and multiples. However, there were only 5 cases of microcephaly among multiple births. Using the robust population-based control group, we calculated the incidence of microcephaly in singletons (1.23 per 10,000 live births) and in multiples (0.67 per 10,000 live births). However, this difference was not statistically significant ($p > 0.05$).

Discussion

Considering the frequency of different congenital anomalies, some are easier to recognize and report, while others are more challenging. Microcephaly is one of the more challenging anomalies, as the major bias in comparisons arises from differences in local numerical definitions of this condition. It has already been pointed out that the definition targets the anthropometric value rather than the (always present) pathological phenotype (Ashwal et al., 2009; Kirby, 2016). Even between countries and surveillance programs with numerically identical definitions, differences may still arise due to variations in formal registration criteria, such as the exclusion of syndromic cases or specific requirements for associated neurologic deficiency (Ashwal et al., 2009; Morris et al., 2016).

During the well-known Zika virus outbreak in Brazil, reported cases of microcephaly varied significantly across different regions, despite the virus being nearly equally present. This highlights that reporting awareness – ranging from under-reporting to over-reporting – can significantly influence the total number of reported anomalies (Kirby, 2016; Rodrigues and Paixaio, 2017).

Population data on microcephaly from European countries have been well presented in the EUROCAT study (Morris et al., 2016). Although incidence rates differ among individual surveillance programs (ranging from 0.4 to 4.3 per 10,000 live births), they remain significantly lower than in the United States, where incidence rates are 2–3 times higher (Hoyt et al., 2018). The main explanation for this difference is the level of definition used: in the U.S., milder criteria (<2 SD, which is approximately <2.5th percentile) are usually applied, while European registries use stricter definitions (Ashwal et al., 2009; Kirby, 2016).

Although population-based registries, like ours, provide reliable and comprehensive data, one key limitation is the inability to conduct follow-up studies, which limits access to more detailed clinical or genetic data.

Our study, based on 21 years of registration data from the Czech Republic, found an average incidence of microcephaly of 1.22 per 10,000 live births, which corresponds to the lower range of European registries reported in the EUROCAT study (Czech data were not included in this particular study).

We specifically analyzed maternal age in microcephaly cases. Maternal age is not widely recognized as a significant risk factor, and many studies do not examine its relationship with microcephaly. When mentioned, the association is typically not significant (Shen et al., 2021). In our study, we did not find a statistically significant difference between the microcephaly and control groups in the mean maternal age. However, a detailed analysis of different maternal age groups revealed a statistically significant distributional difference, where microcephaly was more common in younger and older mothers.

We also observed a significantly higher proportion of female cases (approximately 60%) compared to males (approximately 40%). This female predominance is statistically significant ($p < 0.001$) but remains largely unexplained. Some studies have reported a slightly higher incidence in females (Schuler-Faccini et al., 2016), while others found no significant difference (Rocha et al., 2019). Further research is needed to determine the biological basis for this sex-based discrepancy.

Conclusion

The strength of our population-based study lies in its reliability, as it is based on a compulsory, national surveillance program. However, a major limitation is the lack of follow-up data, as current Czech law prohibits tracking individual cases due to strict anonymity rules.

This study provides the first long-term, population-based estimate of congenital microcephaly in the Czech Republic. Future research should focus on genetic factors, sex differences, and maternal age-related risks to gain deeper insights into the epidemiology and etiology of microcephaly.

Author contribution statement

NF: Designed the study and drafted the initial manuscript. *AŠ:* Collected data from the registers and proposed the types of analyses conducted. *JK:* Performed data processing and conducted biostatistical analyses. *MM:* Performed data processing and conducted biostatistical analyses. *PC:* Reviewed and enriched the manuscript with additional insights. *FL:* Reviewed and enriched the manuscript with additional insights. *AŠ Jr.:* Evaluated the results of the analyses and reviewed and enriched the manuscript.

Patient consent statement

The study is based on individual anonymized data from the official medical registries run by the Institute for Health Information and Statistics of the Czech Republic. The registration process is compulsory under Czech national law, and informed consent is not required.

Data availability statement

The original individual data from official medical registries of the Czech Republic are not available for sharing due to national law. Aggregate datasets may be available upon request from the corresponding author.

Ethical statement

The project received a positive statement from the Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital on April 13th, 2022. ID of the statement: 08090/11; G-22-08.

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Conflict of interest

The authors have no conflict of interest to declare.

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