Cardiology in the Young

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Head circumference in neonates with septal defects

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Abstract

Background: Neurodevelopmental disorders occur in up to 50% of children with CHD. Small head circumference at birth has been associated with impaired neurodevelopment in patients with complex CHD. It is unknown if patients with simple CHD such as septal defects have smaller head circumferences. The objective of this study was to investigate the head circumference at birth in neonates with either an atrial or a ventricular septal defect. *Methods:* This study is part of the Copenhagen Baby Heart Study; a prospective, population-based cohort study of more than 25,000 neonates. The neonates were examined with a comprehensive transthoracic echocardiography within the first 30 days of birth including assessment for atrial or ventricular septal defects. The head circumference at birth in term neonates with septal defects was compared to the head circumference in matched controls, term neonates without septal defects from the same birth cohort. *Results:* Neonates with septal defects ($n = 1{,}030$; 45.2% male; mean birthweight 3,534g ± 483g) had a mean head circumference of 34.8 cm (95% confidence interval 34.7–34.9 cm), compared to neonates without septal defects ($n = 5{,}150$; 45.6% male; mean birthweight 3,546g ± 476g) of 34.7 cm (95% confidence interval 34.7–34.8 cm); p-value 0.07. Mean calculated z-score of head circumferences was 0.05 for neonates with septal defects and −0.01 for neonates without septal defects, $p = 0.07$. Dividing cases into neonates with atrial septal defects, ventricular septal defects, and those without septal defects did not show differences between groups, $p = 0.14$. *Conclusion:* The head circumference in term neonates with septal defects did not differ from matched controls without septal defects.

Introduction

Advances in diagnostics, neonatal care, and surgical management have improved the prognosis for patients with CHD including increased survival rates. Thus, the focus on clinical outcomes has shifted from early mortality toward long-term morbidity.[1] Neurodevelopmental dysfunction is among the most common extracardiac complications in children with complex CHD.[2] Nevertheless, our understanding of the association between patients with minor, acyanotic CHD, including patients with septal defects, and neurodevelopmental outcomes is limited.[3–8] Previous population-based studies have shown that adult patients with an atrial septal defect have a higher incidence of psychiatric issues,[9,10] lower workforce attachment,[11] and cohort studies have shown decreased IQ.[11–13] Neurodevelopmental problems are also seen in patients with ventricular septal defects.[13] Young patients with atrial or ventricular septal defects have also been shown to have a higher burden of hyperactivity and inattention.[14]

The association between small head circumference and impaired neurodevelopment is well-established. The American Heart Association recommends measurements of head circumference to be part of the developmental evaluation in infants with CHD.[15] Head circumference at birth is the most widely available proxy measure of prenatal brain growth[16] and has been associated with neurodevelopmental outcomes from the neonatal period through school age.[17]

Many previous studies on head circumference and neurodevelopmental outcomes focus on complex CHDs, with one study looking at head circumference in different types of CHD in a retrospective, registerbased study.[32] No large, prospective study has investigated isolated cerebral growth specifically in simple cardiac defect. Therefore, we conducted a prospective, population-based cohort study on neonates and focused on those born with common types of simple CHD, i.e. atrial and ventricular septal defects. We aimed to assess the head circumference

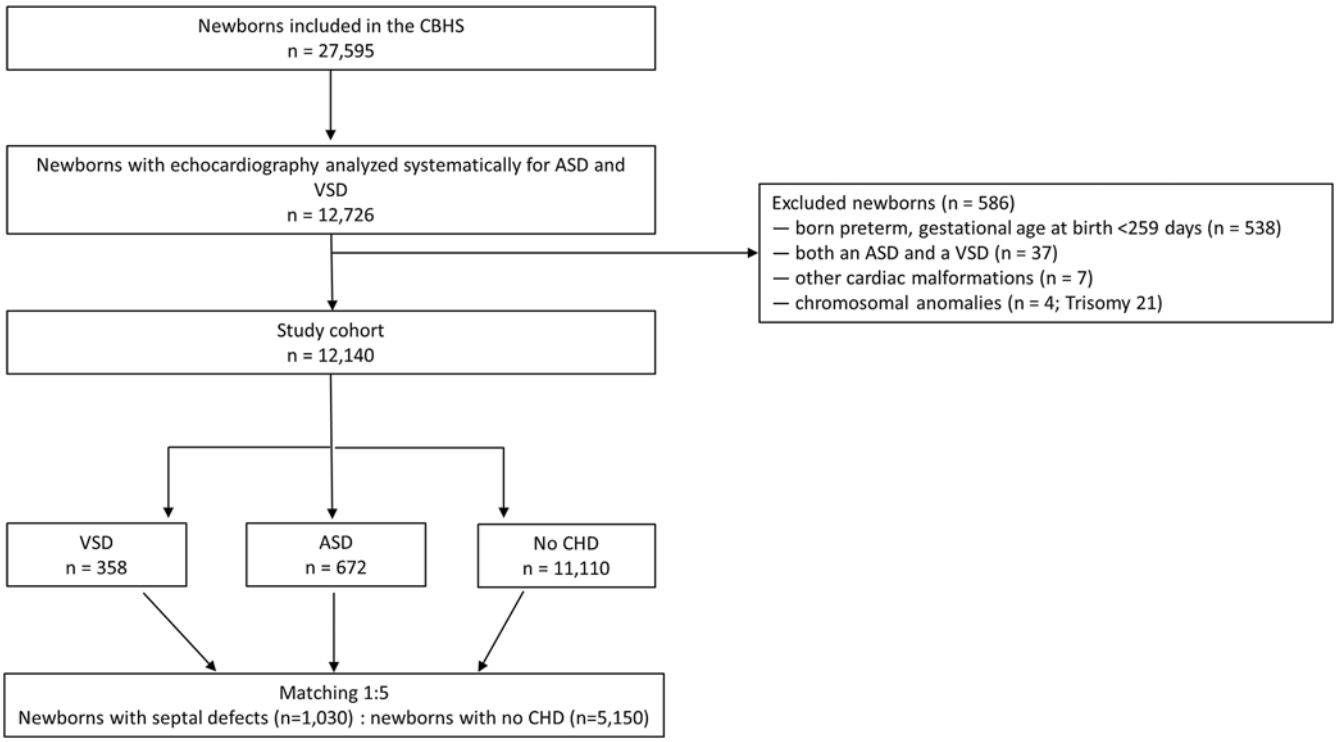

Figure 1. Flowchart over the inclusion process. Abbreviations: ASD = atrial septal defect; CBHS = copenhagen baby heart study; VSD = ventricular septal defect.

at birth as a proxy measure of isolated prenatal cerebral growth in neonates with septal defects, by matching a population cohort on birth weight as a marker of overall fetal growth.

Material and methods

Study design and data collection

This study is part of the Copenhagen Baby Heart Study; a prospective, population-based cohort study including neonates ($n = 27,595$) born at the three largest maternity wards in Copenhagen, Denmark in the period 1 April 2016 to 31 October 2018. All expectant parents were offered inclusion prenatally. The Copenhagen Baby Heart Study was established to study neonatal cardiovascular structure and function, investigate the impact of prenatal exposures on the infant's heart, and determine how congenital cardiac structural and functional abnormalities affect later cardiovascular health. Included neonates underwent neonatal cardiac examination including echocardiography, electrocardiography, and pulse oximetry testing, as well as cord blood samples at birth. Maternal-, pregnancy-, and infant characteristics were collected and stored in the Copenhagen Baby Heart Study database. A detailed description of the study design, the inclusion, and the study cohort has previously been published.[18,19]

Study population

In this specific study, term neonates from the Copenhagen Baby Heart Study diagnosed with atrial or ventricular septal defects based on echocardiographic findings were included. Neonates with gestational age less than 37 weeks (259 days), neonates with concomitant major cardiac malformations,[20] and neonates with known chromosomal anomalies were excluded. Neonates with septal defects were matched to controls without septal defects from the Copenhagen Baby Heart Study. Matching was performed based on the neonates' sex, birthweight, and birth length with a matching ratio of 1:5.

Echocardiography and assessment for septal defects

Neonates included in the Copenhagen Baby Heart Study were examined with a transthoracic echocardiography within the first 30 days after birth by a health professional with sonographic experience. Echocardiographies were analysed for interatrial and interventricular defects using the following two different classification systems.

Echocardiographies were analysed using a newly published algorithm to classify interatrial communications in the oval fossa into three main categories; patency of the foramen ovale, atrial septal defect, and no interatrial communication.[21] The algorithm included six echocardiographic criteria, defined to systematically categorise the findings (see supplementary material for definition of the criteria and algorithm).

Ventricular septal defects were classified according to Soto et al,, as present or not.[22]

Head circumference at birth

Since 1997 it has been mandatory in Denmark to measure the occipitofrontal head circumference for all live births, as a part of the clinical routine examination performed within four hours after birth by a midwife or paediatrician. The information is stored in the Danish Medical Birth Registry,[23] from where these data were extracted. The examination also includes parameters such as APGAR score, birth weight, and birth length.

Statistical analysis

Categorial variables are presented as absolute numbers (percentages) and continuous variables are presented as median values

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(interquartile ranges) or as means (standard deviations). Comparison between neonates with septal defects and matched controls were performed using Student's *t*-test. Z-scores regarding head circumference raw values were calculated for the study population. Furthermore, z-scores of head circumference were analysed for patients and controls according to their gestational age, allocating into groups of gestational ages of week 37 (259 – 265 days), week 38 (266 – 272 days), week 39 (273 – 279 days), week 40 (280 – 286 days), week 41 (287 – 291 days), and week 42 (292 – 298 days), respectively. In a sub-analysis, we investigated differences according to subtype of septal defect, i.e. we compared head circumference in neonates with atrial septal defects, ventricular septal defects, and neonates without septal defects, respectively, using analysis of Variance. p values < 0.05 were considered statistically significant. All analyses were performed using R Studio *v*4.2.0 and StataIC 11.2 (StataCorp LP, College Station, TX).

Results

Study population and descriptive characteristics

The Copenhagen Baby Heart Study included 27,595 infants in total. Details on the Copenhagen Baby Heart Study Cohort and collected data have been published previously.[19] For the present study, we included 1030 neonates with septal defects (672 neonates with an atrial septal defect and 358 neonates with a ventricular septal defect) along with 5150 matched controls. The inclusion process is illustrated in Figure 1. Descriptive characteristics for cases (neonates with septal defects) and controls (neonates without septal defects) are shown in Table 1.

There were no differences between cases and controls regarding maternal age, maternal pre-pregnancy BMI, smoking status, parity, gestational age at birth, or whether the pregnancy was a singleton or twin pregnancy.

Head circumference

Neonates with septal defects had a mean head circumference of 34.8 cm (95% confidence interval 34.7–34.9 cm), compared to neonates without septal defects of 34.7 cm (95% confidence interval 34.7–34.8 cm); p-value 0.07. Regarding mean head circumference z-scores, there were no significant differences between neonates with septal defects and neonates without septal defects (0.05 (95% confidence interval -0.01–0.11) vs. -0.01 (95% confidence interval -0.04–0.02), $p = 0.07$, respectively). In Figure 2A, raw values of head circumference are depicted for neonates with and without septal defects as according to their gestational age. In Table 2, values for head circumference z-scores are listed for neonates with and without septal defects according to their gestational age.

Sub-analyses according to type of septal defect

Dividing cases into neonates with atrial septal defects and ventricular septal defects and comparing to neonates without septal defects did not reveal differences between groups (atrial septal defects 34.8 ± 2, ventricular septal defects 34.9 ± 2, neonates without septal defects 34.7 ± 2, $p = 0.14$). Figure 2B portrays raw values of head circumference according to gestational ages for the three groups.

Table 1. Descriptive maternal and infant characteristics for neonates with and without septal defects

	Neonates with septal defects (n = 1,030)	Neonates without septal defects (n = 5,150)
Maternal characteristics		
Maternal age at birth, years, mean ± SD	31.6 ± 4,5	31.7 ± 4.6
Maternal multiparity, n (%)	441 (42.8)	2152 (41.8)
Missing, n (%)	0	1 (0.02)
Maternal Prepregnancy BMI, kg/m^2, median (IQR)	22.6 (20.5-25.5)	22.6 (20.7-25.3)
Missing, n (%)	4 (0.4)	16 (0.3)
Maternal smoking		
Current smoker, n (%)	29 (2.8)	163 (3.2)
Non-smoker, n (%)	972 (94.4)	4,833 (93.8)
Past smoker, n (%)	5 (0.5)	19 (0.4)
Missing, n (%)	24 (2.3)	135 (2.6)
Neonate characteristics		
Child sex*		
Male, n (%)	466 (45.2)	2346 (45.6)
Female, n (%)	564 (54.8)	2804 (54.4)
Child, Gestational age, d, median (IQR)	282 (274-287)	282 (275-287)
Child, Birth weight*, g, mean ± SD	3534 ± 483	3546 ± 476
Child, Birth length*, cm, mean ± SD	51.6 ± 2.2	51.7 ± 2.1
Singleton/Twin pregnancy Singleton, n (%)	1013 (98.3)	5066 (98.4)

* = matching criteria.
Categorial variables are presented as absolute numbers (percentages) and continuous variables as median values (interquartile ranges) or as means ± standard deviations (SD).
Abbreviations; ASD: Atrial septal defect; VSD: Ventricular septal defect; CBHS; Copenhagen Baby Heart Study; BMI, body mass index; IQR, interquartile range.

Discussion

In a large population-based study, 1030 neonates diagnosed with atrial- or ventricular septal defects by transthoracic echocardiography within the first 30 days of birth did not differ from the matched control group in head circumference.

Numerous studies have investigated potential correlations between CHD and measures of prenatal cerebral growth, given the recognised psychosocial adversities manifested by individuals in their adulthood. These inquiries encompassed evaluations of brain volume,[24,25] prenatal ultrasound metrics,[26,27] fetal MRI studies,[7,24,28] and head circumference at birth.[8,32,29,30,31] The majority of these studies have found an association between CHD and reduced prenatal cerebral growth. Lauridsen et al[29] found brain size and head circumference to be smaller in neonates with CHD compared to neonates without CHD. The differences in head circumference were most pronounced for major CHD, namely univentricular physiology and tetralogy of Fallot, while, in accordance with our study, differences in minor CHD, like septal defects, did not differ significantly. Matthiesen et al,[32] a Danish population-based study, demonstrated that CHD was associated

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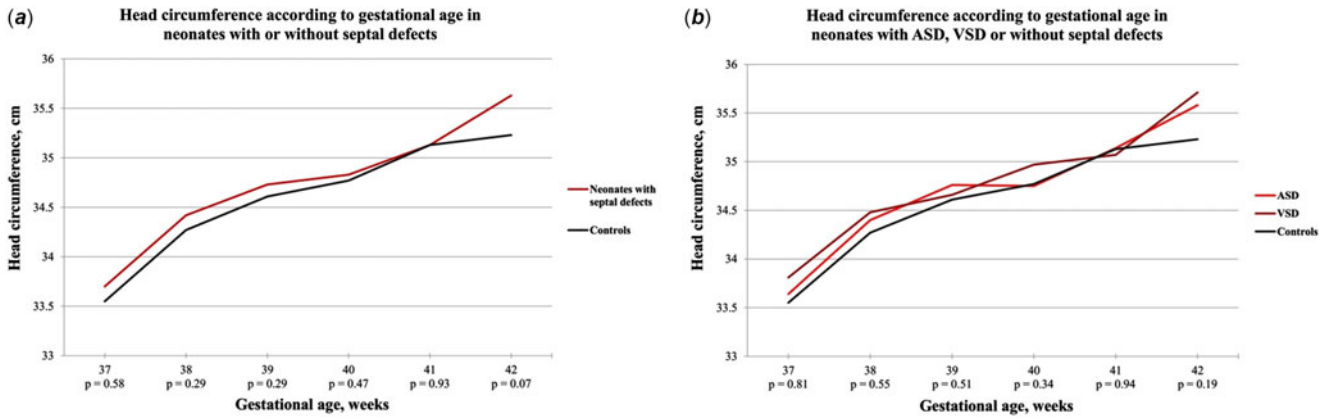

Figure 2. Head circumference raw values. (***a***) Raw values of head circumference for neonates with and without septal defects according to their gestational age. (***b***) Raw values of head circumference according to gestational age for neonates with atrial septal defect, ventricular septal defect, or without septal defect. Abbreviations; ASD = atrial septal defect; VSD = ventricular septal defect.

Table 2. Z-scores for head circumference in neonates with and without septal defects, divided in to groups according to gestational age

Gestational age	Neonates with septal defects (n = 1,030)	Neonates without septal defects (n = 5,150)	p-value
Week 37 (259 – 265 days)	0.08 ± 1 (-0.24; 0.40)	−0.01 ± 1 (-0.12; 0.10)	0.58
Week 38 (266 – 272 days)	0.08 ± 1 (-0.09; 0.24)	−0.02 ± 1 (-0.10; 0.06)	0.29
Week 39 (273 – 279 days)	0.06 ± 0.9 (-0.05; 0.18)	−0.01 ± 1 (-0.07; 0.05)	0.29
Week 40 (280 – 286)	0.04 ± 1 (-0.07; 0.15)	−0.01 ± 1 (-0.06; 0.04)	0.47
Week 41 (287 – 291 days)	−0.01 ± 1 (-0.13; 0.12)	0.001 ± 1 (-0.06; 0.06)	0.93
Week 42 (292 – 298 days)	0.23 ± 0.9 (-0.03;0.49)	−0.04 ± 1 (-0.15; 0.07)	0.07

Data shown as mean ± SD with (95% confidence intervals).

with smaller head circumference, and this was also the case in individuals born with a large ventricular septal defect (requiring surgical closure). In addition, this study identified a larger head circumference relative to their birth weight, indicating asymmetrical prenatal growth.

Most of these earlier studies are either registry-based, with subsequent selection and detection bias, or based on small sample sizes and often highly selected populations, resulting in a limited ability to address the association between specific subgroups of CHD, such as patients with atrial or ventricular septal defects, and measures of prenatal brain growth.[9,27,30,33] In young adults (mean age 25.6 years) with isolated, simple CHD (atrial and ventricular septal defects), there is no change in overall brain size.[13] Our study corroborates those data demonstrating no differences in head circumference at birth.

Studies on the proportionality of prenatal cerebral growth relative to overall growth have been sparse, and the results have been inconsistent.[27,30] Infants with a small head circumference also exhibited low birth weight, indicating that they were symmetrically small.

MRI of the fetal brain ($n = 105$,[24] $n = 35$,[25] $n = 241$[26]) has shown smaller cerebral volumes, decreased cerebral oxygen supply, and delayed cerebral maturation in fetuses with more complex heart defects, which indicates that haemodynamic factors may play an important role in this abnormal development.[24–26] Despite that the brain is of normal size in most patients with septal defects, structural brain changes have been shown in individuals with atrial and ventricular septal defects.[34,35] The cause of impaired neurodevelopment in patients with CHD is largely unknown. In general, studies illuminate the question through different pathophysiological ways; 1) isolated specific cerebral hypo-oxygenation, 2) cerebral hypo-oxygenation combined with additional mechanisms, or 3) shared genetic, environmental, or placental causes of CHD and impaired overall growth. Lauridsen et al [29] demonstrated through measurements of first-trimester bi-parietal diameter and second-trimester head circumference that impaired neurodevelopment in infants with complex CHD begins during second to third trimester in pregnancy.

This study has some limitations, such as sub-optimal echocardiographic images from agitated neonates and sub-optimal visualisation and angulation during echocardiography. To minimise the impact of these difficulties, examinations were primarily performed on calm or sleeping neonates. If this was not possible, parents were advised to reschedule the examination.

All written information was available in several languages and the inability to speak English or Danish was not an exclusion criterion. Nevertheless, language and cultural barriers may still have affected participation rates, as is reflected by the underrepresentation of children born to women with non-Danish backgrounds in the Copenhagen Baby Heart Study cohort. Finally, higher-income households and children with well-educated mothers were over-represented in the Copenhagen Baby Heart Study cohort.[19]

In earlier studies on head circumference and CHD,[8,32,30] the diagnoses of CHD are based on invalidated data from the mandatory national registries. Registries will only include patients where the septal defects have led to symptoms and referral to an echocardiographic examination where the diagnosis has been made. Patients with small defects might not be diagnosed and hence not included in registries. In contrast, a strength of the present study is the fact that the diagnoses of atrial and ventricular septal defects were made by echocardiographic screening in the neonatal period. Due to prenatal inclusion and transthoracic echocardiographic examination of all included neonates after birth, detection bias is limited. The Copenhagen Baby Heart Study

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data provide the unique possibility to study this cohort of neonates, knowing the unselected prevalence of atrial and ventricular septal defects and investigate the association with head circumference at birth.

Conclusion

In a population-based screening study, the head circumference in term neonates with atrial or ventricular septal defects did not differ from neonates without septal defects.

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Competing interests. The authors have no conflicts of interest relevant to this article to disclose.

Ethical standards. The study complies with the Declaration of Helsinki and was approved by the Regional Ethics Committee (H-16001518), Capital Region of Denmark. Written informed consent was obtained from all parents prior to inclusion.

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