Congenital Heart Defects and Measures of Fetal Growth in Newborns with Down Syndrome or 22q11.2 Deletion Syndrome

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Objectives To estimate the association between congenital heart defects (CHD) and indices of fetal growth in Down and 22q11.2 deletion syndromes.

Study design We established 2 Danish nationwide cohorts of newborn singletons with either Down syndrome (n = 670) or 22q11.2 deletion syndrome (n = 155), born 1997-2011. In both cohorts, we analyzed the association between CHD, CHD severity, and indices of fetal growth by multivariable linear regression adjusted for potential confounders. We report mean differences in gestational age specific *z*-scores compared with newborns without CHD.

Results Down syndrome and 22q11.2 deletion syndrome were both associated with lower mean birth weight and head circumference *z*-scores. We found no association between CHD or CHD severity and indices of fetal growth. In Down syndrome, the association between any CHD and the mean difference in head circumference *z*-score was 0.03 (95% CI −0.12, 0.18), and the estimate regarding birth weight *z*-score was 0.09 (95% CI −0.08, 0.25). The corresponding estimates in 22q11.2 deletion syndrome were 0.00 (95% CI −0.33, 0.32) and −0.09 (95% CI −0.45, 0.26).

Conclusions We found no association between CHD and fetal growth measures in newborns with Down syndrome or 22q11.2 deletion syndrome. Thus, in certain subtypes of CHD, the contribution of genetic factors to prenatal growth impairment may be more important than circulatory disturbances. *(J Pediatr 2016;175:116-22)*.

The prevalence of congenital heart defects (CHD) is approximately 6 in 1000 live births,[1] which makes CHD the most common group of major birth defects.[2] The survival of infants with CHD has increased over the last decades, and consequently long-term comorbidities and complications have emerged as major novel research areas.[3] Specifically, neurodevelopmental disorders have been described as the most common and distressing comorbidity in children with CHD.[4,5] The American Heart Association acknowledges a few well-defined risk factors for neurodevelopmental disorders, including infant syndromes and small head circumference.[6] Small head circumference at birth and other measures of impaired prenatal cerebral growth have been consistently associated with both CHD and neurodevelopmental disorders in children with CHD.[4,7,8] The causes of these associations remain incompletely understood; small head circumference may be caused by anomalies of the fetal circulation owing to CHD[9] or in some cases possibly by other mechanisms caused by underlying genetic anomalies.[10] Whereas circulatory perturbations may offer a plausible explanation regarding defects, such as hypoplastic left heart syndrome and transposition of the great arteries,[9] other types of CHD seem less likely to be the direct cause of fetal growth impairment and neurodevelopmental delays. Trisomy 21 is the most prevalent chromosomal disorder worldwide,[11] the most common chromosomal disorder in infants with CHD,[2,12] and a known cause of both small head circumference at birth[10,13] and neurodevelopmental disorders.[11,14-16] The second most prevalent chromosomal disorder in children with CHD is the 22q11.2 deletion syndrome,[2,17,18] likewise a known cause of both small head circumference at birth[19,20] and neurodevelopmental disorders.[21-24] Consequently, infants with Down syndrome, commonly associated with less severe CHDs,[12,25,26] and 22q11.2 deletion syndrome, commonly associated with more severe types of CHD,[18,27] constitute unique populations for the investigation of the associations between CHD, small head circumference, and the underlying causes of neurodevelopmental disorders. However, so far the association between CHD and measures of prenatal cerebral growth in these 2 common syndromes remains unexplored.

We aimed to estimate the association between CHD and head circumference at birth and birth weight in 2 nationwide population-based cohorts of children with Down syndrome or 22q11.2 deletion syndrome. These syndromes constitute chromosomally homogenous populations, which may minimize potential con-

CHD	Congenital heart defects
EUROCAT	European Surveillance of Congenital Anomalies

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founding of the association between CHD and fetal growth measures by unknown or undetected genetic causes.

Methods

We identified all Danish live births in the Danish Medical Birth Registry between January 1, 1997, and December 31, 2011.[28] From the Danish Central Cytogenetic Registry,[18] containing information on all cytogenetic tests performed nationwide in Denmark since 1968, we identified 2 cohorts including all Danish children registered with a confirmative cytogenetic test for either Down syndrome or 22q11.2 deletion syndrome. To maximize the detection of 22q11.2 deletion syndrome, we further included children identified from tests conducted in infants with CHD for research purposes (n = 2478).[18] We linked the mothers and infants to individual level data from the Civil Registration System containing the unique personal identifiers assigned to all people living in Denmark since 1968,[29] the Danish Medical Birth Registry covering all Danish births since 1973,[28] and the Danish National Patient Registry that holds information from all hospital contacts in Denmark since 1977.[30] Reporting to the registries is mandatory nationwide. Newborn singletons with unique personal identifiers and gestational ages at birth within a plausible range of 24-44 weeks were considered eligible.

CHD was identified in the Danish National Patient Register[30] by the codes Q20-Q26 in the 10th edition of the *International Classification of Diseases*.[31,32] Like in previous studies, a few codes, including unspecific codes, codes not related to CHD, and nonstructural CHD codes, were not categorized as CHD (**Table I**; available at www.jpeds.com).[31,32] A previous study validated the use of diagnoses from surgical centers.[32] For this study, we only accepted diagnoses given at the highest specialist level: Surgical contacts (including catheter based interventions) were considered the highest level, admissions to a surgical center without surgery the intermediate level, and admissions to another department of pediatric cardiology the lowest level. We classified CHD into the following mutually exclusive groups of CHD severity according to the European Surveillance of Congenital Anomalies (EUROCAT)[2]: Severe defects included the EUROCAT severity groups 1 and 2 and mild defects included EUROCAT severity group 3 (**Table II**; available at www.jpeds.com). No informed consent was required for this registry-based study. The study was approved by the Danish Data Protection Agency (2013-41-1689).

Newborn weight and head circumference were collected from the Danish Medical Birth Registry. The registration of both measures has been mandatory in Denmark since 1997. All measurements are made by health care professionals at delivery and reported to the register.[28] Records of gestational age were based on ultrasound measurements in close to all pregnancies in 1995.[33] We identified outliers of birth weight equivalent to the most recent US algorithm as estimates of >5 SDs from the median for a given gestational week in term births (in preterm births >3 or <−4 SDs).[34] Estimates based on the last menstrual period were used when ultrasound estimates were identified as outliers. Head circumference values of >5 SDs from the median for a given gestational week were further identified as outliers. We computed head circumference and birth weight *z*-scores for gestational age at birth as the number of SDs from the Danish population mean during the study period.

Calendar year, maternal age, prepregnancy body mass index, smoking, and parity were collected from the Danish Medical Birth Registry.[28] We identified infant non-Western origin and sex in the Danish Civil Registration System[29] (**Table III** and **Appendix**; available at www.jpeds.com). Maternal prepregnancy diabetes, prepregnancy hypertension, and whether the pregnancy was recorded as a high-risk pregnancy during the first trimester (reported by physicians owing to potentially harmful conditions, including social problems and drug or alcohol abuse) were recorded in the Danish National Patient Registry (**Table IV**; available at www.jpeds.com).[30] Newborn extracardiac malformations were also recorded in the Danish National Patient Registry[30] and categorized according to EUROCAT into minor malformations, malformations of the nervous system or the skull, and other major extracardiac malformations (**Table V**; available at www.jpeds.com).[35]

Statistical Analyses

All analyses were carried out separately for the 2 cohorts of children with Down syndrome and 22q11.2 deletion syndrome. In the main analyses, we estimated the associations between CHD, CHD severity, and fetal growth indices. The primary outcome variables were head circumference *z*-score, birth weight *z*-score, and the difference between the 2 measures. We conducted crude and adjusted multivariable linear regression analyses and report the mean *z*-score differences compared with newborns with no CHD. Potential confounders were identified using causal diagrams based on a priori knowledge from previous studies.[36] Dichotomous covariates in the adjusted model included maternal prepregnancy hypertension, diabetes, nulliparity, smoking, infant sex, non-Western origin, and whether the pregnancy was identified as a high-risk pregnancy through the first trimester. Maternal age and prepregnancy body mass index were included as continuous variables. The association with birth year was modeled by cubic splines with 3 knots.

As a reference for the magnitude of the differences in the 2 cohorts, we determined the mean head circumference *z*-scores, mean birth weight *z*-scores, and the mean of the difference between the 2 measures in children with Down syndrome or 22q11.2 syndrome using the live born Danish population during the study period as the reference.[37]

The greatest fraction of missing values for any variable was 8%, except for body mass index, which was available only from 2004. Missing values were handled by multiple imputation according to recent recommendations.[38] We identified important mechanisms behind missing data,