Neurodevelopmental and mental health impairments are now recognized as being among the most prevalent long-term morbidities in children with congenital heart disease (CHD).\(^1,^2\) In 2012, the American Heart Association and the American Academy of Pediatrics published a scientific statement providing recommendations for routine neurodevelopmental evaluation and treatment of children with CHD.\(^1\) The identification of social and communication deficits, potentially related to autism spectrum traits, has only been recently identified as a concern in these patients, however, and there is emerging evidence of an association between CHD and autism spectrum disorders (AuSDs). In 2015, Razzaghi et al\(^3\) reported that children with CHD were more likely to have had a diagnosis of AuSD (crude odds ratio [OR] 4.6). In 2017, in a retrospective, nationwide, population-based case control study, Tsao et al\(^4\) found that children with CHD, compared with a non-CHD group matched for age and sex, had a nearly twofold greater risk of developing AuSD. These and other studies showing a higher risk of autism symptoms in CHD\(^5\) have opened a Pandora’s box of critical questions about whether this association is causal, which subgroups of children with CHD are at greatest risk, and most importantly, what we can do about it.

In this issue of Pediatrics, Sigmon et al\(^6\) sought to quantify the association between CHD and AuSD in a nested 1:3 case control study using the Military Health System administrative database, which includes billing for children in multiple US geographical locations. In this study, children with International Classification of Diseases, Ninth Revision, Clinical Modification codes for a diagnosis of AuSD and a history of CHD were identified. The authors showed significantly increased odds of AuSD in patients with CHD (adjusted OR = 1.3; confidence interval 1.10–1.59). Interestingly, but contrary to the authors’ expectations, the lesions associated with the most significantly higher risk of AuSD were atrial septal defects and ventricular septal defects. CHD types with more severe hemodynamic compromise were generally not significantly associated with a higher risk of autism, although the OR for cases with left heart obstruction lesions including hypoplastic left heart lesions and coarctation of the aorta just reached significance (OR = 1.42; confidence interval 1.04–1.93). One of the strengths of this study is the large number of cases in the database, which allowed the authors to adjust for multiple potential confounders known to be associated with autism, such as genetic syndromes, maternal age and morbidity, perinatal morbidity (ie, low birth weight and short gestation), and neonatal complications, such as epilepsy or birth asphyxia.

Despite the strengths of this study, it raises more questions than answers. As the authors noted, the etiologic pathways that might explain the association between CHD and AuSD are currently unknown. Among the candidates are shared genetic
contributions (eg, overlap between genes with damaging de novo mutations in probands with CHD and autism), fetal and perinatal brain abnormalities (ie, periventricular white matter injury), and patient-specific risk factors such as neonatal and infant epilepsy and preterm birth. The finding that the risk of AuSD is greater in children with forms of CHD that are typically considered to be of relatively modest severity (atrial septal defects and ventricular septal defects) is surprising and requires further investigation. Sigmon et al acknowledge that the limited numbers of cases of rarer and more severe forms of CHD reduce the statistical power to detect their associations with AuSD. The analysis does not match or adjust for catchment area and ethnicity, both of which are potential factors associated with autism. Moreover, the greater number of contacts that children with CHD have with the medical system could cause ascertainment bias. Even when criteria for the diagnosis of AuSD are not met, children and adolescents with CHD often display some degree of social cognition impairment. Survivors of open-heart surgery in infancy have more difficulty than the general population in processing social cues, such as facial emotional expressions, and in theory of mind (ie, understanding people’s intentions and beliefs). As with youth born preterm, autism-related traits in CHD might display a unique behavioral phenotype related to their etiologic mechanisms and comorbidities. The interplay between autism and related traits in the CHD population and their genetic and environmental underpinnings provides many avenues for future research. In the meantime, patients with CHD should undergo routine serial neurodevelopmental assessments, including screening for autism spectrum symptoms, beginning as early as possible to provide the opportunity for intervention. Older children with CHD also can benefit from screening for social and communication difficulties at critical junctures, including school entry and preadolescence. A proactive approach will lead to better developmental trajectories and improved quality of life for youth with CHD.

**ABBREVIATIONS**

AuSD: autism spectrum disorder
CHD: congenital heart disease
OR: odds ratio

**REFERENCES**
