Congenital Heart Defects and Developmental and Other Psychiatric Disorders
A Danish Nationwide Cohort Study

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Background—We examined the risk of psychiatric in-patient admissions and out-patient visits among Danish patients with congenital heart defects (CHD).

Methods and Results—Using the Danish National Registry of Patients, we identified CHD patients born January 1, 1977, to January 1, 2002. For each patient, we randomly selected 10 population-comparison cohort members from the Danish Civil Registration System, matched by sex and birth year. We computed cumulative risk and hazard ratios (HRs) of time to first psychiatric in-patient admission or out-patient visit identified in the Danish Psychiatric Central Registry and adjusted for parents’ educational level and parents’ psychiatric morbidity. We identified 6927 CHD patients. At 15 years of age, the cumulative risk of psychiatric admissions or out-patient visits was 5.9% (95% confidence interval [CI], 5.2%–6.6%) among CHD patients. The HRs for CHD patients and comparison cohort members aged 0 to 14 years were 1.8 (95% CI: 1.5–2.1) for males and 2.5 (95% CI: 2.0–3.1) for females. For patients aged 15 to 30 years, the HRs were 1.6 (95% CI: 1.2–2.0) for males and 1.0 (95% CI: 0.8–1.3) for females. Congenital heart defect patients, both with and without invasive therapeutic interventions or extracardiac defects or syndromes, had a higher risk of psychiatric in-patient admissions or out-patient visits than comparison cohort members. After restriction of the comparison cohort to patients with diabetes mellitus or asthma (n=2554), the HR was 1.41 (95% CI: 1.07–1.85) for patients aged 0 to 14 years and 0.70 (95% CI: 0.52–0.94) for patients aged 15 to 30 years.

Conclusion—Congenital heart disease patients with or without invasive therapeutic interventions are at increased risk of developmental and other psychiatric disorders, which seem to develop earlier than in patients with diabetes mellitus or asthma. (Circulation. 2011;124:00-00.)

Key Words: heart defects, congenital ■ epidemiology ■ prognosis ■ mental health
Study Cohorts and Design
We based this cohort study on data from nationwide registries. We used the Danish National Registry of Patients (DNRP) to identify all infants born between January 1, 1977, and January 1, 2002, who received a primary diagnosis of CHD at any age. The DNRP contains information on all hospital admissions in Denmark and includes patients’ civil registration numbers, dates of admission and discharge, surgical procedures, and up to 20 discharge diagnoses coded by physicians according to the ICD. The 8th edition of ICD was used until the end of 1993, and the 10th edition thereafter. ICD-8 codes used to identify CHD patients were 746 to 747 (except for 746.7 and 747.5–747.9, which are not specific to CHD) and ICD-10 codes Q20-Q26 (except for Q26.5-Q26.6, also not specific to CHD). International Classification of Diseases, 10th revision, codes were categorized according to the corresponding ICD-8 codes. Patients were grouped on the basis of their first primary CHD diagnosis. Diagnoses of patent ductus arteriosus were included only for infants whose gestational age was ≥37 completed weeks according to the Danish Medical Birth Registry.16

For each patient, we identified 10 population-comparison cohort members from the Danish Civil Registration System, matched by sex and birth year. The Civil Registration System has kept electronic records on date of birth, date of emigration, and date of death for all Danish residents since 196817 on the basis of a unique personal identifier assigned to every Danish citizen and used in all public Danish registries. The personal identifier permits unambiguous data linkage. We assessed the educational level of the parents via linkage to the Integrated Database for Labor Market Research.18 We categorized the highest educational level recorded for the parents during the study period as primary education, secondary education, or higher education.

In addition to the CHD codes provided above, we used the following codes to identify diagnoses of extracardiac defects (ECDs) and chromosomal abnormalities in the DNRP: ICD-8 codes 310.40 to 310.41, 310.5, 311.40 to 311.41, 311.5, 312.40 to 312.41, 312.5, 313.40 to 313.41, 313.5, 314.40 to 314.41, 314.5, 315.40 to 315.41, 315.5, and 740.99 to 759.99; and ICD-10 codes Q70.0 to Q79.9. The study encompassed diagnoses given at any time after birth. In accordance with a guideline from the European Surveillance of Congenital Anomalies (EUROCAT), we disregarded isolated minor defects such as subluxation or unstable hip, cryptorchidism, torticollis, or protuberant ears.19 We obtained data on gestational age from the Danish Medical Birth Registry and defined preterm birth as gestational length <37 weeks.

Chronic disease per se in children has been associated with an increased likelihood of psychiatric disorders.20 To compare the incidence of psychiatric hospitalization or out-patient visits among CHD patients with the incidence after other chronic diseases, in a subanalysis we restricted the comparison cohort to individuals with a hospital diagnosis of diabetes mellitus or asthma recorded in the DNRP. We used the following codes to identify these diagnoses: ICD-8 codes 249 to 250, ICD-10 codes E10 to E14, G63.2, H360, or N083 (diabetes mellitus), and ICD-8 code 493 or ICD-10 codes J45 to J46 (asthma).

Psychiatric Morbidity
We linked the CHD and the comparison cohorts to the Danish Psychiatric Central Registry (DPCR),21 which contains electronic records on all in-patient admissions to Danish psychiatric hospitals since 1970 and on out-patient visits since 1995. We used DPCR data to identify psychiatric outcomes, including developmental disorders, for the cohorts, as well as indicators of maternal or paternal psychiatric morbidity.13 Psychiatric diseases were coded in the DPCR according to ICD-8 until December 31, 1993, and according to ICD-10 thereafter. Parental psychiatric morbidity was defined by the presence of any psychiatric diagnosis (ICD-8: 290–315; ICD-10: F00–F.99) before the birth date of the CHD patient or control individual. We restricted this indicator to diagnoses occurring before the birth of a child with CHD because having a critically ill child is likely to increase parental risk of psychiatric morbidity.

Because a substantial part of Danish psychiatric healthcare is provided in out-patient clinics,22,23 patient follow-up for psychiatric care began on January 1, 1995, when out-patient contact data became available in the registry. Study outcomes included any psychiatric diagnosis (F.00–F.99) and specific psychiatric disorders of special interest in the CHD population: psychotic disorders (F.20–F.29),24 pervasive developmental disorders (F.84),2 specific developmental disorders of speech, motor function, and learning (F.80–F.83),25 ADHD (F.90),4 and any degree of mental retardation (F.70–F.79).6 The study was approved by the Danish Data Protection Agency, whose role is to protect the privacy of individuals whose data are recorded in Danish registries. No informed consent was required for this study.

Data Analysis
Follow-up of CHD patients and the comparison cohort began on the date of CHD diagnosis or on January 1, 1995, whichever came later, and continued until initial psychiatric diagnosis, emigration, death, or January 1, 2007, whichever occurred first. Patients hospitalized for psychiatric disorders before the start of follow-up were excluded to avoid capturing prevalent disease. The cumulative incidence of psychiatric admissions and out-patient visits as of age 15 was computed assuming death to be a competing risk.25

We used Cox proportional regression analysis to compute hazard ratios (HRs) of time to first psychiatric diagnosis among CHD patients compared with the general population cohort, using age as the underlying time scale. We adjusted for parents’ educational level and history of psychiatric morbidity. Analyses were stratified by age, sex, and surgical or catheter-based therapeutic intervention versus no intervention and repeated after excluding patients and individuals in the comparison cohort who were born preterm or with ECDs (including syndromes or chromosomal anomalies). The age cutoff at 15 years correlates with the transition from pediatric to adult cardiological care in Denmark. We did a subanalysis using a general population comparison cohort restricted to individuals with diabetes mellitus or asthma, followed up from the time of diagnosis. Individuals with missing data on parental educational level were excluded from the analyses (~3%). We graphically verified the assumption of proportional hazards. Analyses were performed using the Stata 10.1 package (StataCorp LP, College Station, TX).

Results
We identified 6927 CHD patients, 49% male, who were born between January 1, 1977, and January 1, 2002, and were alive on January 1, 1995, or later. The most frequent types of CHD diagnoses were ventricular septal defect and atrial septal defect. Extracardiac defects or syndromes were present in 19.5% of the CHD patients and in 3.3% of the general population cohort members. Among CHD patients, 9.1% were born preterm compared with 5.0% of general population cohort members (Table 1).

For CHD patients, the overall cumulative risk of psychiatric admissions or out-patient clinic visits up to age 15 was 5.85% (95% confidence interval [CI], 5.15%–6.61%). The overall HR for psychiatric admission or out-patient clinic visit among CHD patients compared with the general population cohort was 1.60 (95% CI: 1.44–1.77). The risk of admissions for psychotic disorders, developmental disorders, ADHD, or any degree of mental retardation was also elevated among CHD patients (Table 2).

Compared with the general population cohort, the risk of psychiatric disorders for CHD patients in the younger age group (0–14 years) was increased both for patients with and without the need for surgery or catheter-based intervention.
Patients who did not undergo surgery or a catheter-based intervention were at increased risk in the older age group, as well, compared with the general population cohort (HR: 1.34 [95% CI, 1.08–1.66]). Both male and female CHD patients under 15 years of age were at increased risk of psychiatric disorders (male HR, 1.76 [95% CI: 1.48–2.09]; female HR, 2.49 [95% CI: 2.00–3.11]). Male CHD patients aged 15 to 30 years were also at increased risk of psychiatric disorders (HR, 1.57 [95% CI, 1.22–2.01]). In contrast, we did not observe an elevated risk of psychiatric disorders in female patients aged 15 to 30 years compared with the general population cohort (HR, 1.04 [95% CI, 0.84–1.30]). When patients and controls with ECD or syndromes and those born preterm were excluded from the analysis, the estimates were not substantially changed although some reduction of risk was seen in the group aged under 15 years (Table 3).
hospital-diagnosed diabetes mellitus (n=272) or asthma (n=2296), including combinations of the 2 conditions, the CHD patients’ risk of psychiatric disorders, compared with this chronic diseases cohort, was increased in the younger age group (0–14 years) (HR, 1.41 [95% CI, 1.07–1.85]), and decreased in the older age group (15–30 years) (HR, 0.70 [95% CI, 0.52–0.94]). When we did separate analyses with only diabetes patients or asthma patients in the chronic diseases cohort, the HRs did not vary (data not shown).

Discussion
To the best of our knowledge, this population-based study is the first to examine clinically verified psychiatric disorders, including developmental disorders, among CHD patients. It extends the findings of previous studies that reported an increased risk of neurodevelopmental impairment and behavioral problems among CHD patients followed at treatment centers.

A number of earlier studies have reported findings of neurodevelopmental problems in terms of slightly impaired cognitive function, speech and language difficulties, and impaired motor skills among CHD patients. Similarly, our study found an increased risk of out-patient clinic visits or hospital admissions for mental retardation and specific developmental disorders of motor, speech, and learning among CHD patients compared with the general population cohort. The risk of these disorders in our CHD population was about 1.6% at 15 years of age (Table 2). Increased risk of ADHD among CHD patients has also been reported recently. In a follow-up study of 380 preschool-aged children who had undergone cardiac surgery with a wide range of complexity, Gaynor et al reported that 30% of children in the study cohort scored in the clinically significant range for inattention

<table>
<thead>
<tr>
<th>Table 2. Hazard Ratios and Cumulative Incidence of Psychiatric In-Patient Admission or Outpatient Visits for Specific Psychiatric Disorders Among Congenital Heart Defect Patients Compared With the Population Comparison Cohort</th>
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</thead>
<tbody>
<tr>
<td>HR (95% CI)*</td>
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<tr>
<td>15-Year Cumulative Incidence, % (95% CI) All</td>
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<tr>
<td>Any psychiatric disorder</td>
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<tr>
<td>Psychotic disorders (eg, schizophrenia)</td>
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<tr>
<td>Pervasive developmental disorders (eg, autism spectrum disorders)</td>
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<tr>
<td>Specific developmental disorders (speech, motor, and learning disorders)</td>
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<tr>
<td>Attention deficit hyperactivity disorder</td>
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<td>Mental retardation (mild to severe)</td>
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</tbody>
</table>

Data are presented for all study subjects and for a subgroup of patients and comparison cohort members born at term without extracardiac defects.

*Adjusted for paternal psychiatric disorder, maternal psychiatric disorder, paternal educational level, and maternal educational level.
†Including syndromes and chromosomal anomalies.
‡Observed No. of psychiatric inpatient admissions or outpatient visits among congenital heart defect patients.

<table>
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<tr>
<th>Table 3. Hazard Ratios of a Psychiatric In-Patient Admission or Out-Patient Visit Among Congenital Heart Defect Patients Compared With the Population Comparison Cohort by Age, Gender, and Surgery or Catheter-Based Intervention</th>
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<tbody>
<tr>
<td>HR by Age Group in Years (95% CI)*</td>
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<td>&lt;15 y</td>
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<tr>
<td>15–30 y</td>
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<tr>
<td>All n‡ HR (95% CI)</td>
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<td>All</td>
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<tr>
<th>Gender</th>
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<tr>
<td>Male n‡ HR (95% CI)</td>
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<tr>
<td>152 1.76 (1.48–2.03)</td>
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<tr>
<td>71 1.57 (1.22–2.01)</td>
</tr>
<tr>
<td>91 1.47 (1.19–1.83)</td>
</tr>
<tr>
<td>51 1.54 (1.15–2.06)</td>
</tr>
</tbody>
</table>

| Female n‡ HR (95% CI)                         |
| 100 2.49 (2.00–3.10)                         |
| 90 1.04 (0.84–1.30)                          |
| 55 1.89 (1.42–2.51)                          |
| 71 1.06 (0.83–1.35)                          |

<table>
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<tr>
<th>Surgery or catheter-based intervention</th>
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<tr>
<td>Yes n‡ HR (95% CI)</td>
</tr>
<tr>
<td>150 2.22 (1.86–2.65)</td>
</tr>
<tr>
<td>71 1.15 (0.90–1.48)</td>
</tr>
<tr>
<td>76 1.64 (1.29–2.08)</td>
</tr>
<tr>
<td>48 1.05 (0.78–1.41)</td>
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</tbody>
</table>

| No n‡ HR (95% CI)                             |
| 102 1.72 (1.41–2.10)                         |
| 90 1.34 (1.08–1.66)                          |
| 70 1.55 (1.22–1.98)                          |
| 74 1.41 (1.11–1.78)                          |

Data are presented for all study subjects and for a subgroup of patients and comparison cohort members born at term without extracardiac defects.

*Adjusted for: paternal psychiatric disorder, maternal psychiatric disorder, paternal educational level, and maternal educational level.
†Including syndromes and chromosomal anomalies.
‡Observed No. of psychiatric inpatient admissions or outpatient visits among congenital heart defect patients.
and 22% in the clinically significant range for impulsivity on the ADHD Rating Scale IV, Preschool Version. In contrast, only 4% to 7% of preschool children were reported to have these conditions in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Although our study also detected an increased risk of ADHD among CHD patients compared with the general population cohort, the cumulative incidence of approximately 1% at age 15 (Table 2) seems low in light of the DSM-IV estimates. There are at least 2 explanations for this: (1) ICD-10 criteria for the ADHD diagnosis are stricter than DSM-IV criteria27 and (2) the high mortality of children in the CHD cohort, compared with the general population cohort, results in a lower cumulative incidence of ADHD visits because death is a competing risk.

Our finding of a higher occurrence of pervasive developmental disorders among CHD patients compared with the general population cohort (Table 2) agrees with the work of Gaynor et al. They found higher scores for pervasive developmental problems in a follow-up study of preschool children who had undergone cardiac surgery compared with normative data.4

The increased occurrence of psychotic disorders that we identified among CHD patients compared with the general population cohort may be due, at least in part, to the 22q11.2 deletion syndrome (also known as velocardiofacial syndrome or DiGeorge syndrome) that is associated with CHD.28 One third of all individuals with 22q11.2 deletion syndrome develop schizophrenia-like psychotic disorders.24 However, the HR remained increased after exclusion of CHD patients and population comparison cohort members with ECD or chromosomal anomalies. This indicates that additional mechanisms may be relevant. On the other hand, 22q11.2 deletion syndrome may present without typical dysmorphic features and the syndrome is known to be under-recognized.29

We did not identify an increased risk of hospital admissions for psychiatric care, nor for attendance at out-patient psychiatric clinics among female patients in the older age group (15–30 years, Table 3). Van Rijen et al.7 who assessed emotional and behavioral problems in adults with CHD using the Young Adult Self-Report, found that an increased proportion of female CHD patients (20–27 years of age) scored in the psychopathological range compared with normative data. In contrast, Utens et al.30 using the same assessment instrument, found that more male CHD patients aged 22 to 25 years, but not female patients, scored in the psychopathological range compared with normative data. However, the findings of these studies reflect the prevalence of psychiatric morbidity in a given age group and not the incident cases of psychiatric hospitalization that our analyses are based on, a difference that hampers direct comparison. We did, for example, find similar incidences of first-time psychiatric hospitalization in the female CHD cohort compared with the female general population cohort in the older age group (15–30 years). This, however, does not preclude different prevalences of psychiatric disorders in the 2 cohorts because psychiatric disorders diagnosed in childhood may potentially recur or adopt a chronic clinical course. Several factors may have contributed to our findings of increased occurrence of first-time diagnosis of psychiatric disorders among male but not among female CHD patients in the older age group (15–30 years), compared with the male and female general population cohorts. In the general population, determinants of the onset of psychiatric disorders may vary according to age and gender as do the overall incidence and diagnostic categories of psychiatric disorders.31 Thus, the incidence of childhood psychiatric disorders is higher among boys, who mainly have developmental disorders. In contrast, the incidence of psychiatric disorders in adolescence is higher among females, who mainly have anxiety disorders.31 This age–gender interaction likely relies on both biological and social factors, but specific mechanisms are unknown, as is their relevance in the presence of CHD.

Possible mechanisms underlying the risk of psychopathology among CHD patients include ECD, genetic syndromes, and preterm birth, as these factors have all been associated with psychiatric disorders.12,32–34 However, after excluding patients with these characteristics, we still identified an association between CHD and psychiatric disorders. We found an increased risk of psychiatric disorders among CHD patients in the younger age group (0–14 years) but not in the older age group (15–30 years) compared with diabetes and asthma patients. This may reflect a more prominent role of impaired neurological development in the CHD psychopathology than in the psychopathology of asthma and diabetes patients. Thus, neurodevelopmental disorders such as ADHD and autism emerge during childhood27 whereas the depression and anxiety disorders associated with childhood diabetes mellitus and asthma typically emerge in adolescence and young adulthood.35,36

Abnormal intrauterine blood flow among patients with complex CHD,37 as well as white matter lesions38 or cerebral hypoxia, may impair neurological development and increase the risk of psychiatric disorders.39,40 Treatment-related factors that may cause neurological damage include cerebral embolization41 or reduced cerebral blood flow due to an inadequate cardiopulmonary bypass technique.42 However, these factors did not explain the increased risk of psychiatric disorders found among CHD patients who did not undergo surgical treatment. In addition, given that need for surgery is related to CHD severity, this finding also indicates that severity is not strongly related to the risk of psychiatric disorders. In a study of children undergoing cardiac surgery, Hövels-Gürich et al. noted that children with Tetralogy of Fallot are not at increased risk of behavioral problems compared with children with ventricular septal defects.43 The results from an Irish study of children with a range of cyanotic and acyanotic defects who underwent either corrective or palliative surgery highlight the sometimes greater relevance of family processes (eg, parenting style, maternal mental health, and worry) rather than disease or surgical factors, in predicting behavioral outcomes in this context.11 Thus, interactions among several biological and psychological risk factors are likely.

The validity of our estimates depends on accurate coding of CHD and psychiatric diagnoses. The positive predictive value of CHD diagnoses in the DNRP is reported to be high,44 and any misclassification of overall CHD status is small and independent of future psychiatric morbidity. The CRS allowed a population-based design with complete long-term follow-up of vital status and linkage to the DPCR. The
validity of the DPCR also is high, reflected in validation studies of diagnoses such as schizophrenia, affective psychoses, and childhood autism.45,46 We did not have data on out-patient contacts for psychiatric disorders before January 1, 1995. If CHD patients with out-patient contacts for psychiatric disorders before January 1, 1995, were more likely diagnosed with psychiatric disorders later in life, we may have overestimated the occurrence of first time psychiatric disorders among CHD patients in the older age group (15–30 years) compared with the general population cohort. However, given previous research demonstrating an increased risk of neuropsychological development disorders5,5,6 and psychological maladjustment,11,17 as well as the strength of the associations in our study, we do not believe that this potential bias explains our results. Psychiatric hospitalization is a recognized outcome measure in research on psychiatric disorders with high validity.48

We considered important factors known to be associated with psychiatric disorders in our analyses (ie, age, gender, parental psychiatric history, social status, preterm birth, and ECD or chromosomal anomalies).12 However, potential residual confounding from, eg, subclinical parental psychiatric disorders or confounding from unknown risk factors for psychiatric disorders may have biased the results of our observational study.

We lacked detailed clinical information, such as the severity of CHD. Yet our data indicated an elevated risk of psychiatric admission both for patients with and without surgical/catheter-based interventions. This indicates that our findings are not strongly affected by defect severity, which is in line with the findings of others.41 Because of the continuous development of CHD treatment, results from different eras cannot be readily compared. This should be considered before generalizing the study results for 15- to 30-year-old patients to the prognosis for patients born and diagnosed today. Long-term results are inherently based on patients diagnosed several years previously, stressing the need for a continuous monitoring of the outcome of CHD patients.

In conclusion, we identified increased risks of psychiatric disorders, including developmental disorders, among male and female CHD patients <15 years of age and among male patients aged >15 years compared with a general population cohort. Patients who did not undergo surgery or catheter-based interventions were also at increased risk. When patients and controls with ECD or chromosomal abnormalities and those born preterm were excluded, the risk remained elevated. Nonetheless, the majority of CHD patients appear to have a favorable mental health prognosis.

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Disclosures
None.

References

**CLINICAL PERSPECTIVE**

Studies focusing on a wide range of congenital heart defects (CHDs) have reported associations with mild cognitive impairment, speech and language difficulties, impaired motor skills, attention deficit hyperactivity disorder, and autism-like disabilities. These disabilities may cross the boundaries of many clinical disciplines including neurology, pediatrics, and psychiatry, depending on referral practices. In this study we examined the incidence of psychiatric hospitalization or out-patient visits among Danish patients with CHD compared with a general population cohort. We focused on psychiatric admissions and out-patient contacts overall and on contacts for specific mental disorders in accordance with the overall pattern of neurobehavioral sequelae described in the CHD population, as well as relevant genetic risk factors. The overall risk of a first-time psychiatric diagnosis was elevated compared with the general population cohort, whether or not a cardiac therapeutic intervention had occurred. In the age range for potential pediatric cardiac follow-up (<15 years of age), the risk was increased for both male and female patients. Among those aged 15 to 30 years who receive treatment in an adult cardiac clinic, only males were at increased risk for a first-time psychiatric diagnosis compared with the general population cohort. Because our study only considered first-time psychiatric diagnoses, our results cannot exclude the possibility that more adult female CHD patients may have mental health issues at a given time (prevalent disease) compared with females in the general population. Our study indicates the importance of addressing mental health issues in optimal CHD follow-up and care.
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