Risk of Lifetime Psychiatric Morbidity in Adults With Atrial Septal Defect (from a Nation-Wide Cohort)

Camilla Nyboe, PhD[a,*], Sebastian Udholm, PhD[a], Signe Holm Larsen, PhD[a], Charlotte Rask, PhD[b], Andrew Redington, MD[c], and Vibeke Hjortdal, PhD[d,e]

In this nation-wide cohort study we report the first long-term results of the association between having a atrial septal defects (ASD) on psychiatric disorders and use of psychotropic agents. Through population-based registries we included Danish individuals born before 1994 who received an ASD diagnosis between 1959and 2013. We used Cox proportional hazards regression and Fine and Grey competing risk regression to estimate the risk of receiving a psychiatric diagnosis and use of psychotropic medicine compared with a gender and age matched background population cohort. In 2,277 patients with a median follow-up from ASD diagnosis of 23.4 years (range 0.2 to 59.3 years) we found ASD patients to have a higher risk of psychiatric disorders (adjusted hazard ratio [HR]: 3.9; 95% confidence interval [CI] 3.4 to 4.5) compared with the comparison cohort and a cumulative incidence of using psychotropic agents 30 years after the ASD diagnosis of 47.4% (95% CI: 40.3 to 55.1) in the ASD patients and 25.5%, (95% CI: 23.5 to 27.8) in the comparison cohort. Diagnosis of the ASD before the age of 15 years (adjusted HR: 3.4; 95% confidence interval: 2.0 to 4.0) and surgical correction of the defect (HR: 1.5 (95% CI: 1.2 to 1.8), p <0.0001) had a higher risk than those with an ASD diagnosis after the age of 15 years and those with transcatheter closure of the defect. In conclusion, ASD patients had increased long-term risk of psychiatric disorder and use of psychotropic agents compared with a gender and age matched general population controls. **(Am J Cardiol 2020;128:1−6)**

Chronic diseases have a significant impact on mental health in both children[1−4] and adults.[5,6] Children who underwent surgery for congenital heart disease (CHD) have an increased risk of impaired executive and cognitive function and an increased prevalence of autism.[7−11] Diminished neuroaxonal development and metabolism in fetuses with CHD is possibly related to altered cerebral blood flow[12] and lower tissue oxygenation[13] and in adulthood, micro embolization through a persistent foramen ovale (PFO) is associated with increased risk of stroke.[14] In patients with CHD, risk factors for psychiatric disease exist both inherently from genetic associations, physiologic alterations during pregnancy, or through exposure to both physiological and psychological factors. Indeed, the risk of psychiatric disease is substantially increased in patients with CHD,[15] but is unknown in patients with isolated atrial septal defects (ASD). In these patients, prenatal blood-flow is not significantly altered, and the long-term impact is often considered benign. However, recent studies have shown that ASD patients are not as unaffected as previously suggested.[16−20]

Methods

We used several sources of data in this study. Diagnostic, anthropometric, and demographic data were obtained from the Danish National Patient Registry. The publically funded Danish healthcare system is free of charge and equally accessible for all Danes. Each Dane has since 1968 been provided with a unique personal identification number enabling linkage of data from all hospitals. Data are gathered in nationwide public registries where registration is mandatory for all hospitals and outpatients clinics. Information on dates of birth, migration, and death is identified in the Danish Civil Registration System.[21] The Danish National Patient Registry contains information on all hospital admissions in Denmark, dates of admission and discharge, surgical procedures, and discharge diagnoses coded according to the International Classification of Disease (ICD).[22] The 8th edition was used until 1993 after which the 10th version was used.

In the Danish National Patient Registry we identified all patients born before 1994 and diagnosed with ASD from the beginning of the registration period in 1977 and up to 2013. The cutoff at 1994 was chosen to ensure follow up into adulthood. Two physicians validated the hospital records of all ASD patients eligible for validation, and

[a]Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Child and Adolescent Psychiatry, Psychiatry, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Pediatrics, Cincinnati Children's Hospital, Cincinnati, Ohio; [d]Department of Cardiothoracic Surgery, Copenhagen University Hospital, Rigshospitalet and Institute of Clinical Medicine, Copenhagen University, Copenhagen, Denmark; and [e]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark. Manuscript received January 28, 2020; revised manuscript received and accepted April 24, 2020.

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*Corresponding author: Tel.: +45 20959903; fax: +45 78453079

E-mail address: camilla@nyboe.nu (C. Nyboe).

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excluded those with PFO or concomitant congenital heart disease, thus only including patients with an ASD. During the medical record review, a small number of patients with ASD diagnosis dates and/or ASD closure dates recorded before the initiation of the Danish National Patient Registry were identified. Thus, dates of diagnoses of included subjects ranges from 1959 and up to January 1, 2013. The study population has previously been used in studies investigating mortality[19] and work participation[20] in ASD patients.

The second source of data was from a population of patients with an ASD diagnosed before the age of 15 years and the diagnosis given between 1963 and 1974. These patients were identified by an experienced physician in the years 1970 to 1974, by review of inpatient and outpatient hospital records in all Danish medical and pediatric departments.[23] The personal registration number of patients alive in 1968 was manually identified, and their diagnoses were translated to ICD-10 codes. Patients who did not survive or migrated prior to receiving a personal identification number (n = 5) were excluded. Follow-up was continued until January 1, 2018. We excluded patients with concomitant congenital heart disease, except those registered as unspecified congenital heart disease or patent ductus arteriosus (n = 3). For every verified ASD patient, 10 persons from the general population were matched on gender and birth year using the Danish Civil Registration System. Diagnosis date of the ASD patients was used as the date of matching between ASD patients and their controls. The matching date was used to eliminate the risk of immortal bias in the ASD patients.

We used the Danish National Psychiatry Registry to identify all hospital admissions with a psychiatric diagnosis since 1970 and up to January 1, 2018.[24] Outpatient contacts were added from 1995. Outcomes included all psychiatric diagnoses in the range F10 to F49 and F60 to F98 with corresponding ICD-8 codes. Outcomes are henceforth listed as ICD-10 codes due to the structured organization even though matching ICD-8 codes are included. Outcomes were divided into child psychiatric disorders (F70 to F98) with diagnoses predominantly given in childhood or adolescence, and adult psychiatric disorders (F10 to F49 and F60 to F69) with diagnoses given in adulthood. Use of psychotropic agents was identified in the Danish National Prescription Registry. The Danish National Prescription Registry contains information on all prescription drugs redeemed from Danish community pharmacies since 1994.[25] It contains individual level information on the Anatomical Therapeutic Codes on prescriptions dispensed to all individuals including residents at care facilities. We used redeemed prescriptions for psychiatric medicine including antipsychotic medicine, anxiolytics, antidepressants, hypnotics and psychological stimulants. Information on indication for medicine use is not available in the Danish National Prescription Registry. However, in Denmark these psychotropic agents cannot be obtained without a prescription.

We used the Danish National Patient Registry to identify all hospital contacts prior to the ASD diagnosis, or matching date for the comparison cohort, with cardiac disease, diabetes, pulmonary disease, cerebrovascular disease and diseases in the Charlson Co-morbidity Index. We adjusted the Charlson Co-morbidity Index to exclude those elements thought to be a part of the causal pathway between ASD and psychiatric disease, i.e. cerebrovascular events. In the Danish National Education Registry we gathered information of highest completed education for both the ASD patients and the comparison cohort since 1981. The presence of a syndrome in either the patients or the comparison cohort was registered using the Danish National Patient Registry. Following codes were used: ICD-8 (310.40 to 41, 310.5, 311.40 to 41, 311.5, 312.40 to 41, 313.40 to 41, 313.5, 314.40 to 41, 314.5, 315.40 to 41, 315.5, and 740.99 to 759.99) and ICD-10 (DQ00.0 to DQ99.9). Psychiatric morbidity was identified in the parents for both ASD patients and the comparison cohort. We also used the Danish National Patient Registry to identify patients with an epilepsy diagnosis (ICD-10 DG40 and correlating ICD-8 codes).

We used Cox proportional regression analysis to compute hazard ratios (HR) for first hospital contact (in- or outpatient contacts in the hospital) with psychiatric disease among patients with ASD beginning at time of birth comparing them with the comparison cohort, using age as the underlying time scale. Analyses were stratified by age at diagnosis in a separate analysis, and were adjusted for gender, diagnosed syndromes, Charlson Co-morbidity Index and parents' psychiatric morbidity. We graphically verified the assumption of proportional hazards with log-minus-log plots. Using Fine and Gray competing risk regression we estimated the cumulative incidences of psychiatric disease in patients and compared them with the comparison cohort. In these calculations, subjects with diagnosed syndromes in both cohorts were excluded.

We used Fine and Gray competing risk regression to calculate 10- and 20-year cumulative incidences in patients with child psychiatric disorders. In these analyses, we included only patients born after 1969, where the Danish National Psychiatric Registry was initiated, and we excluded subjects with diagnosed syndromes.

Use of psychotropic agents was analyzed in patients diagnosed with an ASD after 1994, where the Prescription Registry was initiated. Cox proportional regression analysis was used to compute hazard ratios for first redeemed prescription for psychiatric medicine since the ASD diagnosis compared with the comparison cohort. The date of diagnosis was used as start of follow up for the comparison cohort. Age was used as an underlying time scale and the analyses were adjusted for gender, diagnosed syndromes, Charlson Co-morbidity Index, epilepsy and parents' psychiatric morbidity.

All analyses were performed using Stata 15/StataCorp LP, TX.

This study was approved by The Central Denmark Region Research Committee (1-16-02-570-18) and the National Board of Health (j.nr. 7-604-04-2/193/KWH).

Results

We identified 4,445 patients born before 1994 and diagnosed with an ASD before 2013, in the Danish National Patient Registry. Of those, 609 had a concomitant congenital heart disease and were excluded. The hospital record was missing in 651 patients leaving 3,286 patients for

Table 1
Baseline characteristics

Variable	ASD patients	Controls	ASD versus controls
	n = 2,277	n = 22,756	
Diagnosed <15 years	1,063 (47%)		
Age at diagnosis, mean +/-sd (years)	22.6 ± 24.9		
Diagnosed after 1994	1,070 (47%)		
Surgery	1,067 (47%)		
Catheter treatment	481 (21%)		
Age at closure, mean +/- sd (years)	29.3± 21.9		
Female	1,384 (61%)	13,834 (61%)	
Diagnosed syndrome	65 (3%)	5 (0.02%)	<0.0001
Chronic lung disease	181 (8%)	1,024 (5%)	<0.0001
Diabetes mellitus	116 (5%)	790 (3%)	<0.0001
Pulmonary heart disease	123 (5%)	52 (0.2%)	<0.0001
Hypertension	262 (12%)	1,661 (7%)	<0.0001
Ischemic heart disease	325 (14%)	1,212 (5%)	<0.0001
Cerebrovascular events	180 (8%)	613 (3%)	<0.0001
Arrhythmia	514 (23%)	715 (3%)	<0.0001
Highest education reported*	2,073 (92%)	21,030 (92%)	
Basic	755 (33%)	5,775 (25%)	<0.0001
Youth	170 (7%)	2,452 (11%)	<0.0001
Vocational	652 (29%)	6,998 (31%)	0.065
Higher	496 (22%)	5,811 (26%)	0.0002
Short cycle	69 (3%)	833 (4%)	0.14
Medium cycle	274 (12%)	3,254 (14%)	0.005
Long cycle	153 (7%)	1,724 (8%)	0.17
Data missing on education	204 (8%)	1,726 (8%)	0.3
Maternal psychiatric disorder	193 (12%)	1,730 (11%)	0.23
Paternal psychiatric disorder	132 (8%)	1,274 (8%)	0.68

* Proportion calculated from patients alive at the age of 18 years (ASD patients n = 2,253, controls n = 22,707).

validation. After exclusion of patients with a PFO or no ASD, a total of 2,277 patients with a confirmed ASD diagnosis and a matched comparison cohort of 22,756 were included in the study. Co-morbidity was in general more common in the ASD patients than in the comparison cohort, and specifically the number of arrhythmias and cerebrovascular events were higher, as expected from previous studies (Table 1).[16–20]

Median follow-up was 23.4 years (range 0.2 to 59.3 years). The ASD patients had an overall increased risk for psychiatric morbidity compared with the comparison cohort, HR: 3.9 (95% CI 3.4 to 4.5) and an increased cumulative incidence compared with the comparison cohort (Figure 1). The proportion of patients using prescription psychiatric medicine was similarly increased in the ASD group with a cumulative incidence 20 years after the ASD diagnosis of 26% (95% CI: 20.1 to 31) versus 12% (95% CI: 10.9 to 13.7) in the comparison cohort. This increased to almost half of the ASD patients 30 years after the ASD diagnosis (47% (95% CI: 40.3 to 55.1)) compared with a quarter of the patients in the comparison cohort (26%, (95% CI: 23.5 to 27.8)).

Patients diagnosed after 1969 (n = 1,070) and their matched comparison cohort had a total of 110 and 126 diagnoses for psychiatric disease in childhood and adolescence respectively, after patients and controls with acknowledged syndromes were excluded (n = 24). Autism was diagnosed more often in the ASD patients (n = 13 (1.2%)) than in the comparison cohort (n = 6 (0.06%)), p <0.0001. At the age of 10 years, there was an almost 10-fold increase in cumulative incidence of psychiatric morbidity in the ASD patients (3.9% (95% CI 3.0 to 5.2)) compared with the comparison cohort (0.2% (95% CI: 0.14 to 0.3), p <0.0001). When the age of 20 years was reached the numbers were 7.4% (95% CI: 6.0 to 9.1), in the ASD patients, and 0.3% (95% CI: 0.25 to 0.46), in the comparison cohort (p <0.0001). The diagnoses were evenly distributed between ICD10 F70 to 78: Mental Retardation ((n = 41), F80 to 89: Disorders of Psychological Development (n = 33), and F90 to 98: Behavioral and Emotional disorders (n = 43) in the ASD patients.

Patients with an ASD had a significantly increased risk of adult psychiatric disorders compared with the comparison cohort (Table 2), however there was not an overall increased risk of receiving a new psychiatric diagnosis if closure of the defect was performed: HR 1.3 (95% CI: 0.9 to 1.7), p = 0.116) compared with those with no closure. Those who had surgery performed had a higher risk of developing psychiatric morbidity, (HR: 1.5 (95% CI: 1.2 to 1.8), p <0.0001) than those with transcatheter closure when adjusted for gender and age at closure. There was no statistically significant difference in risk of any psychiatric morbidity between male and female ASD patients, HR 0.92 (95% CI: 0.73 to 1.7, p = 0.76).

Patients diagnosed before the age of 15 years of age had a significantly higher risk of a psychiatric diagnosis compared with those who received their ASD diagnosis after the age of 15 years, HR: 3.4 (95% CI: 2.0 to 4.0), p <0.0001, and with increased cumulative incidence in the ASD patients with an early ASD diagnosis (Figure 2). This was also the case for those having closure performed with

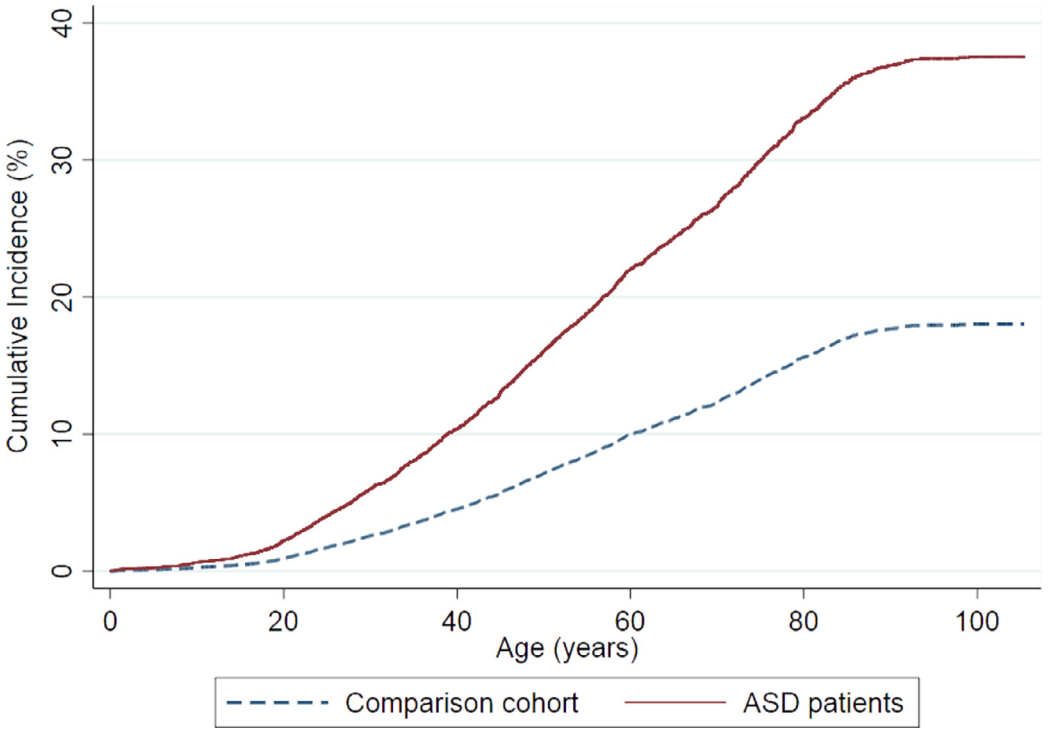

Figure 1. Competing risk of any psychiatric morbidity (child and adult) in patients with atrial septal defect and the comparison cohort from birth and until end of follow up with death as a competing risk. Patients with diagnosed syndromes are excluded.

Table 2
Risk of receiving a psychiatric diagnosis or using psychotropic agents

Variable	ASD patients	Controls	ASD patients versus controls	
			HR (95% CI)	p
Risk of psychiatric diagnosis	(n = 2,277)	(n = 22,756)		
All adult psychiatric diseases F10-49 + F60-69	312 (14%)	1,577 (7%)	2.8 (2.4-3.3)	<0.0001
Psychoactive substance use F10-19	58 (2.5%)	368 (1.6%)	1.9 (1.3-2.8)	<0.0001
Schizophrenia/psychosis F20-29	46 (2%)	194 (0.8%)	3.0 (2.0-4.5)	<0.0001
Mood affective disorders F30-39	114 (5%)	684 (3%)	2.9 (2.2-3.7)	<0.0001
Emotional disorders F40-49	179 (8%)	731 (3%)	3.8 (3.1-4.6)	<0.0001
Personality disorders F60-69	55 (2.4%)	318 (1.4%)	2.2 (1.6-3.1)	<0.0001
Risk of psychiatric medicine prescription	(n = 1,070)	(n = 10,812)		
All prescription medicine	326 (30%)	2,612 (24%)	1.5 (1.3-1.8)	<0.0001
Antipsychotic medicine	76 (7%)	503 (5%)	1.6 (1.2-2.3)	<0.0001
Antidepressant medicine	206 (19%)	1,534 (14%)	1.6 (1.3-1.9)	<0.0001
Anxiolytic medicine	97 (9%)	854 (8%)	1.6 (1.2-2.1)	0.002
Hypnotic medicine	124 (12%)	1,018 (9%)	1.6 (1.3-2.2)	0.002
Psycho stimulant medicine	20 (2%)	116 (1%)	1.7 (1.01-2,8)	0.043

Psychiatric disease and use of prescription psychiatric medicine in ASD patients compared with the comparison cohort (hazard ratios for psychiatric diagnosis were adjusted for gender, syndrome, Charlson Co-morbidity Index, and parents psychiatric morbidity. Hazard ratios for psychiatric medicine prescriptions were adjusted for additionally adjusted for epilepsy).

either transcatheter procedure or surgery before the age of 15 years compared with those who had the procedures performed after the age of 15 years: HR 3.7 (95% CI: 3.0 to 4.6), p <0.0001. However, patients diagnosed with an ASD after the age of 15 years still had an increased risk of psychiatric morbidity compared with their comparison cohort (HR: 1.5 (95% CI: 1.2 to 1.8)). When only including patients diagnosed with an ASD after the age of 25 years, the risk compared with the comparison cohort diminished, but remained significantly increased (HR: 1.3 (95% CI: 1.03 to 1.7), p = 0.027).

Discussion

In this nationwide cohort study, we found the overall risk of psychiatric morbidity in patients with an ASD diagnosis was significantly increased. We also found that earlier age at diagnosis and closure procedure is associated with psychiatric morbidity later in life. Although the ASD is present from birth in all the ASD patients, it seems that either the knowledge of having a heart diagnosis or having a closure procedure performed earlier in life impacts the risk of impaired mental health. The reason for this is not clear,

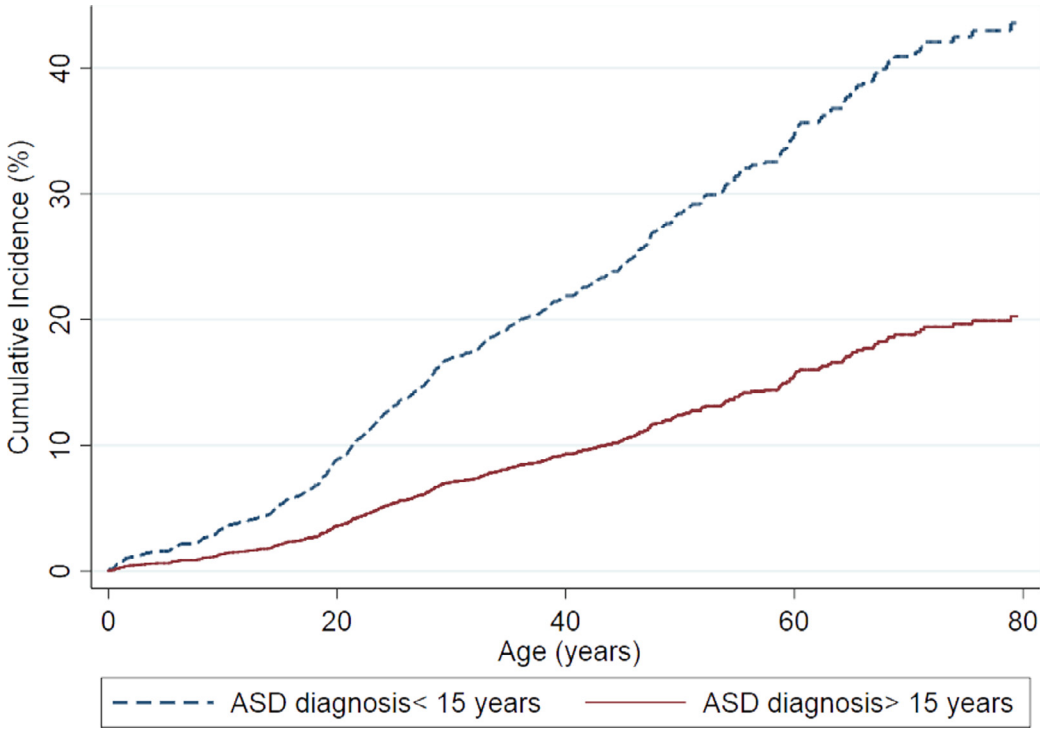

Figure 2. Competing risk of adult psychiatric morbidity in patients with an atrial septal defect diagnosed before the age of 15 years compared with patients diagnosed with an atrial septal defect after the age of 15 years. Death is used as a competing risk. Patients with diagnosed syndromes are excluded.

although we might speculate that the impact of 'the burden of diagnosis', with its associated parental and patient anxiety, has a greater impact in childhood than in adult life. It is noteworthy however, that even patients with an ASD diagnosis after the age of 25 years had an increased risk of psychiatric morbidity compared with the comparison cohort, suggesting that other aspects than a psychosocial cause if present. Environmental factors cannot explain all the differences observed, as those who underwent transcatheter closure had a significantly lower risk of psychiatric disorder than those who underwent surgical closure.

While traditionally not considered a 'chronic disease', some of the psychological burdens associated with a diagnosis of ASD appear to be similar to that observed in cancer, diabetes and asthma.[2,4,26] Self-reported and interview based studies found that almost half the patients with diabetes had psychiatric issues, predominantly depression and anxiety. The incidence was highest closer to the diabetes diagnosis and associated with poor regulation of the diabetes. Kullowatz et al. found similarly a high prevalence of depression and anxiety in patients diagnosed with asthma in childhood.[5] Depression and anxiety are both issues, along with cognitive impairment, language- and motor development that are central in the studies conducted on children and adults with chronic disease. In our study, we also found an increased risk of anxiety and depressive disorders, but also found increased risk of psychoses such as schizophrenia, and personality disorders and child psychiatric disorders.

This wide variety of diagnoses again suggests more than a simple psychosocial cause to the burden of psychiatric disease in ASD patients. Further studies should be directed towards understanding potential underlying genetic associations, the direct impact of surgery,[27] and the possible impact of 'subclinical' cerebral embolization from intermittent right to-left shunting.

We know that mothers using specific types of mood stabilizing medicine (SSRI) have an increased risk of giving birth to children with congenital heart disease and have therefore adjusted for parents' psychiatric disease. The risk appears especially increased for ASD and VSD.[28,29] The risk of psychiatric disease in patients with ASD could be increased solely because their parents more often experience psychiatric disease or because the mother's use of SSRI also increases the risk of development of psychiatric disease in the child.[30] Unfortunately, we do not have information on all parents due to missing linkage between the parents and their children in the oldest of the patients. We do not have comprehensive data on use of psychiatric medicine in the parents, and so could not adjust for this. Furthermore, the incidence of mental health problems in the parents may have been underestimated, given the era constraints of the databases used. The Central Psychiatry Registry only includes outpatient data from 1995. We have chosen to include hospital diagnoses from the initiation of the registry knowing, that outpatient diagnoses are only included after this time. We do not expect any differences between outpatient and in-hospital diagnoses between the ASD cohort and the comparison cohort and therefore believe there to be an equal underestimation of the results if there is any bias.

Finally, the validity of the diagnoses in the registries is essential and dependent of the physicians generating the data. The ASD diagnoses in this study have been manually validated leaving very little error. Not all psychiatric diagnoses have been validated, but those that have been, are in general considered to have very good validity.[23] Some diagnoses, such as some genetic disorders, asymptomatic ASDs

and diabetes mellitus, may be under diagnosed, thus not figuring in the registries. We believe the free for all and easy accessible Danish hospital service minimizes this risk.

Patients with an ASD have an increased risk of psychiatric disorders compared with the general population. This increased risk persists throughout life, but is highest when the ASD is diagnosed in childhood, and when closed surgically rather than by transcatheter intervention. Our data indicate the importance of early vigilance, education of parents and teachers, and lifelong monitoring for psychiatric vulnerability in adult patients with a diagnosis of ASD.

Author Contribution

Camilla Nyboe: Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft preparation, Project administration **Sebastian Udholm.**: Conceptualization, Methodology, Writing - Review and editing. **Signe Holm Larsen**: Visualization, Methology, Writing - review and editing. **Charlotte Rask**: Visualization, Methology, Writing - review and editing.**: Andrew Redington:** Visualization, Methology, Writing - review and editing **Vibeke Hjortdal** Conceptualization, Methodology, Writing - Reviewing and Editing, Resources, Supervision, Funding acquisition.

Disclosures

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1. Cadman D, Boyle M, Szatmari P, Offord DR. Chronic illness, disability, and mental and social well-being: findings of the Ontario Child Health Study. *Pediatrics* 1987;79:805–813.
2. Kovacs M, Goldston D, Obrosky DS, Bonar LK. Psychiatric disorders in youths with IDDM: rates and risk factors. *Diabetes Care* 1997;20:36–44.
3. Spijkerboer AW, Utens EM, Bogers AJ, Verhulst FC, Helbing WA. Long-term behavioural and emotional problems in four cardiac diagnostic groups of children and adolescents after invasive treatment for congenital heart disease. *Int J Cardiol* 2008;125:66–73.
4. Butwicka A, Fendler W, Zalepa A, Szadkowska A, Zawodniak-Szalapska M, Gmitrowicz A, Mlynarski W. Psychiatric disorders and health-related quality of life in children with type 1 diabetes mellitus. *Psychosomatics* 2016;57:185–193.
5. Kullowatz A, Kanniess F, Dahme B, Magnussen H, Ritz T. Association of depression and anxiety with health care use and quality of life in asthma patients. *Respir Med* 2007;101:638–644.
6. Voinov B, Richie WD, Bailey RK. Depression and chronic diseases: it is time for a synergistic mental health and primary care approach. *Prim Care Companion CNS Disord* 2013;15.
7. Gaynor JW, Nord AS, Wernovsky G, Bernbaum J, Solot CB, Burnham N, Zackai E, Heagerty PJ, Clancy RR, Nicholson SC, Jarvik GP, Gerdes M. Apolipoprotein E genotype modifies the risk of behavior problems after infant cardiac surgery. *Pediatrics* 2009;124:241–250.
8. Miatton M, De Wolf D, Francois K, Thiery E, Vingerhoets G. Behavior and self-perception in children with a surgically corrected congenital heart disease. *J Dev Behav Pediatr: JDBP* 2007;28:294–301.
9. Miatton M, De Wolf D, Francois K, Thiery E, Vingerhoets G. Neuropsychological performance in school-aged children with surgically corrected congenital heart disease. *J Pediatr* 2007;151:73–78. 78 e71.
10. Hovels-Gurich HH, Konrad K, Skorzenski D, Minkenberg R, Herpertz-Dahlmann B, Messmer BJ, Seghaye MC. Long-term behavior and quality of life after corrective cardiac surgery in infancy for tetralogy of Fallot or ventricular septal defect. *Pediatr Cardiol* 2007;28:346–354.
11. Asschenfeldt B, Evald L, Heiberg J, Salvig C, Østergaard L, Dalby RB, Eskildsen SF, hjortdal VE. Neuropsycholoical status and structural brain imaging in adults with simple congenital heart defects closed in childhood. *JAHA* 2020. accepted for publication.
12. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL Jr., Guizard N, McGrath E, Geva J, Annese D, Dunbar-Masterson C, Trainor B, Laussen PC, du Plessis AJ. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation* 2010;121:26–33.
13. Lauridsen MH, Uldbjerg N, Henriksen TB, Petersen OB, Stausbol-Gron B, Matthiesen NB, Peters DA, Ringgaard S, Hjortdal VE. Cerebral oxygenation measurements by magnetic resonance imaging in fetuses with and without heart defects. *Circ Cardiovasc Imaging* 2017;10:e006459.
14. Purandare N, Oude Voshaar RC, McCollum C, Jackson A, Burns A. Paradoxical embolisation and cerebral white matter lesions in dementia. *Br J Radiol* 2008;81:30–34.
15. Olsen M, Sorensen HT, Hjortdal VE, Christensen TD, Pedersen L. Congenital heart defects and developmental and other psychiatric disorders: a Danish nationwide cohort study. *Circulation* 2011;124:1706–1712.
16. Nyboe C, Olsen MS, Nielsen-Kudsk JE, Johnsen SP, Hjortdal VE. Risk of Pneumonia in Adults With Closed Versus Unclosed Atrial Septal Defect (from a Nationwide Cohort Study). *Am J Cardiol* 2014;114:105–110.
17. Nyboe C, Olsen MS, Nielsen-Kudsk JE, Hjortdal VE. Atrial fibrillation and stroke in adult patients with atrial septal defect and the long-term effect of closure. *Heart* 2015;101:706–711.
18. Karunanithi Z, Nyboe C, Hjortdal VE. Long-term risk of atrial fibrillation and stroke in patients with atrial septal defect diagnosed in childhood. *Am J Cardiol* 2017;119:461–465.
19. Nyboe C, Karunanithi Z, Nielsen-Kudsk JE, Hjortdal VE. Long-term mortality in patients with atrial septal defect: a nationwide cohort-study. *Eur Heart J* 2018;39:993–998.
20. Nyboe C, Fonager K, larsen ML, Andreasen JJ, Lundbye-Christensen S, Hjortdal V. Effect of atrial septal defect in dults on work participation (from a nation wide register-based follow-up study regarding work participation and use of permanent social security benefits. *Am J Cardiol* 2019;124:1775–17779.
21. Schmidt M, Pedersen L, Sorensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–549.
22. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health* 2011;39(7 Suppl):30–33.
23. Videbaek J, Laursen HB, Olsen M, Hofsten DE, Johnsen SP. Long-term nationwide follow-p study of simple congenital heart disease diagnosed in otherwise healthy children. *Circulation* 2016;133:474–483.
24. Mors O, Perto GP, Mortensen PB. The Danish psychiatric central research register. *Scand J Public Health* 2011;39(7 Suppl):54–57.
25. Kildemoes HW, Sorensen HT, Hallas J. The Danish national prescription registry. *Scand J Public Health* 2011;39(7 Suppl):38–41.
26. Ross L, Johansen C, Dalton SO, Mellemkjaer L, Thomassen LH, Mortensen PB, Olsen JH. Psychiatric hospitalizations among survivors of cancer in childhood or adolescence. *N Engl J Med* 2003;349:650–657.
27. Hsia TY, Gruber PJ. Factors influencing neurologic outcome after neonatal cardiopulmonary bypass: what we can and cannot control. *Ann Thorac Surg* 2006;81. S2381-2388.
28. Furu K, Kieler H, Haglund B, Engeland A, Selmer R, Stephansson O, Valdimarsdottir UA, Zoega H, Artama M, Gissler M, Malm H, Norgaard M. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *BMJ* 2015;350:h1798.
29. Grigoriadis S, VonderPorten EH, Mamisashvili L, Roerecke M, Rehm J, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Ross LE. Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best evidence. *J Clin Psychiatry* 2013;74:e293–e308.
30. Liu X, Agerbo E, Ingstrup KG, Musliner K, Meltzer-Brody S, Bergink V, Munk-Olsen T. Antidepressant use during pregnancy and psychiatric disorders in offspring: Danish nationwide register based cohort study. *BMJ* 2017;358:j3668.