



Small atrial septal defects are associated with psychiatric diagnoses, emotional distress, and lower educational levels

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Abstract

Objective: For the first time, we wish to assess the psychiatric burden in adult patients living with small, unrepaired atrial septal defects (ASD) using register-based data, combined with self-reported measures on levels emotional distress and educational status.

Design: A descriptive study using both the unique Danish registries and validated psychiatric questionnaires and scales, including: The Symptom Checklist, Whiteley-7, and Brief Illness Perception Questionnaire.

Patients: Adult patients with small, unrepaired ASD, diagnosed between 1953 and 2011.

Outcome Measures: Number of register-based psychiatric diagnoses. Additionally, symptoms of anxiety, depression, somatization, health anxiety, illness perception, and levels of educational attainment compared to age- and gender-matched individuals from the reference group.

Results: We identified 723 Danish patients with a small, unrepaired ASD. Approximately 17% of the patients eligible for inclusion had one or more psychiatric diagnoses. The most common diagnoses were neurotic, stress-related, and somatoform disorders. A total of 140 patients (mean age 33 years) was included for examination of their mental health using psychiatric questionnaires and scales. Patients with small ASD had higher scores of depression and anxiety when compared to the reference group (0.57 ± 0.67 vs 0.39 ± 0.52 ; $P < .001$). Furthermore, patients reported more symptoms of somatization (0.51 ± 0.48 vs 0.34 ± 0.39 ; $P < .001$). Finally, a higher percentage of patients with an unrepaired ASD had no education beyond high school when compared to the reference group (33.3% vs 14.3%; $P < .001$) and a smaller proportion of patients had completed a short-cycle higher education (6.5% vs 16.1%; $P = .002$).

Conclusion: Patients with a small, unrepaired ASD in adult life have more symptoms of anxiety, depression, and somatization compared to the reference group. Furthermore, fewer patients had no education beyond high school. These results support the guidelines that adults with small ASD warrants regular lifelong follow-up in specialized clinics aware of not only adverse somatic outcome but also rates of depression and anxiety.

KEYWORDS

atrial septal defect, epidemiology, grown-up congenital heart disease (GUCH), mental health, psychiatric disorders, simple lesions

1 | INTRODUCTION

Management of children born with a congenital heart disease has improved over the last five decades and today more than 90% of these patients can expect to reach adulthood.^{1,2} As a consequence, long-term outcome of this growing adult population has become an important issue, with increasing focus on neurodevelopmental and mental health concerns. Indeed, increased prevalence of especially depressive and anxiety disorders was recently documented in adults with congenital heart disease (ACHD).^{3,4}

One of the most common congenital heart lesions in adults is atrial septal defects (ASD). Usually, large and symptomatic defects are offered closure, while patients with asymptomatic ASD without right ventricular enlargement, thromboembolic complications, or with a pulmonary to systemic flow ratio less than 1.5, are typically left untreated. Patients with small, unrepaired ASD were once believed to be as healthy as the general population; however, this notion has been called into question. We have demonstrated that patients with a small, unrepaired ASD that persists into adult life have increased risk of premature death (mean age of death was 63 years), more chronic diseases, worse functional capacity, higher levels of stress, and lower scores on self-assessed physical function compared to the general population.⁵⁻⁹

In sum, growing up with an ASD diagnosis, repaired or not, doubtlessly have far-reaching consequences not just limited to somatic health problems. Supportive of this notion, a novel study concluded that ASD was the most common congenital malformation in ACHD patients associated with depression and anxiety.¹⁰ Given the fact that the presence of depression is associated with higher mortality in ACHD patients, it seems important to address mental health issues in patients with small ASD.^{4,10}

We hypothesized that a substantial proportion of patients with small, unrepaired ASD had a psychiatric diagnosis, and higher scores on self-reported psychiatric measures when compared to a reference group. In this present study we, therefore, aimed to further explore the psychiatric burden and emotional distress in these patients by examining their number of register-based psychiatric diagnoses and levels of self-reported emotional symptoms. In addition, we also examined their educational attainment in comparison to age- and gender-matched individuals from a reference group.

2 | METHODS

2.1 | Study design

This is an add-on study to a previous nationwide descriptive cohort study of all adult Danish patients diagnosed with an unrepaired ASD.⁸ The cohort was identified using the Danish National Patient Registry (DNPR).^{5,6} The DNPR contains information on all patients admitted to Danish hospitals or seen in outpatient clinics, including: dates of admission and discharge, surgical procedures, and discharge diagnoses coded according to the International Classification of Disease (ICD). The ASD diagnosis was validated by two independent

clinicians through review of hospital records. Patients with defect closure, pulmonary arterial hypertension, or Eisenmenger syndrome, and persistent foramen ovale were excluded, thereby presumably leaving only patients with a small, unrepaired ASD. Data on mental health problems were obtained from both the unique Danish registries and self-reported questionnaires.

2.2 | Register data

The DNPR was used to identify all hospital admittances (since 1977) and outpatient clinic contacts (since 1994) with a history of psychiatric and somatic comorbidity for both patients included in this study, patients excluded based on the exclusion criteria used in the main study,⁸ and patients who did not respond to or declined the invitation letter for the present study. The ICD-8 was used until 1993 after which the ICD-10 was used. The psychiatric diagnoses were grouped according to the ICD-10 categories as follows: F10-19, F20-29, F30-39, F40-49, F50-59, F60-69, F70-79, F80-89, and F90-98 with matched ICD-8 codes included.

2.3 | Study sample and self-reported questionnaires

Every patient in Denmark diagnosed with an unrepaired ASD, aged between 18 and 65 years, were invited to Aarhus University hospital to undergo assessment of their mental health using validated self-report questionnaires. Enrolment was conducted from December 2015 to June 2018. This is, as mentioned, an add-on study, thereby conforming to the predetermined inclusion and exclusion criteria designed for the main study.⁸ In brief, patients with severe mental or psychiatric disorder, other congenital heart disease (except patent ductus arteriosus), persistent foramen ovale, and previous ASD closure were excluded. For the present study, we used data collected by validated self-reported questionnaires on health anxiety, emotional distress, unspecific somatic symptoms, and illness perception (see measures below) as well as data on self-reported general health and educational status. All included ASD patients received questionnaires identical to the reference group and they received a brief instruction before answering. Patients completed the questionnaire while at the hospital. Unless asked for question clarification, there was no intervention from the investigators.

2.4 | Reference group for comparison

We compared our study sample to a reference group using data from the Danish study of Functional Disorders (DanFunD).¹¹ The DanFunD study is a major longitudinal population-based study focusing on medically unexplained symptoms and functional disorders. This study is conducted in a random sample of the Danish adult general population, including 9656 adult citizens in Denmark. A random sample of 1120 individuals, matched on gender and age to our study sample and in a ratio of 8:1 individual per patient was drawn from this cohort.

2.5 | Self-reported measures

Anxiety and depression (emotional distress) were assessed on subscales of the Symptom Checklist-92 (SCL-92), namely SCL-dep and SCL-anx.¹² All items were rated on a 5-point Likert scale ranging from 1 (not at all) to 5 (a lot), with higher scores indicating more symptoms. The SCL-dep subscale has 13 items (scale range 13-65) and the SCL-anx subscale has 10 (scale range 10-150). Sum scores were subsequently transformed into a scale between 0 (no symptoms) to 4 (severe symptoms). Additionally, we used the SCL-8 to measure the risk of suffering from anxiety or depression.¹³ It combines eight anxiety and depression items from the SCL where answers on single items are dichotomized between 0 (corresponding to a score of 1 or 2) and 1 (corresponding to a score of 3, 4, or 5) so that scores range from 0 to 8. Dichotomized scores ≥ 5 points corresponds to a 60% or more risk of suffering from anxiety or depression.¹⁴ SCL-92 is thoroughly tested, and have been successfully used to test for emotional distress in patients with chronic fibromyalgia and neuropathic pain.¹⁵

Health anxiety was assessed by Whiteley-7 (WI-7).¹⁶ WI-7 is a seven-item tool, with each item scored on a 5-point scale ranging from 0 (not at all) to 4 (a lot) (scale range 0-28). Thus, higher scores indicate more severe health anxiety. WI-7 is extensively used and has shown good sensitivity and specificity in screening for hypochondriasis and mental illness in new neurological patients.¹⁷⁻¹⁹

Somatization was measured by the SCL-92 subscale, SCL-som. The SCL-som consists of 12 items, each scored on a 5-point Likert scale (scale range 12-60), with higher scores indicating more symptoms. Like the SCL-subscales sum scores were subsequently transformed into a scale between 0 (no symptoms) to 4 (severe symptoms).

Illness or symptom perception was measured by the Brief Illness Perception Questionnaire (BIPQ), which has been widely used in a range of illnesses.²⁰ The questionnaire consists of eight items scored on a 10-point scale and measures core dimensions of illness perception. The total score ranges from 0 to 70 with higher scores indicating more negative illness or symptom perceptions. The BIPQ have been used and tested in a wide variety of patients with chronic diseases, including chronic pulmonary obstructive disease, cancer, and heart failure.²¹⁻²³

Educational levels: Four groups representative of the Danish educational system was used to index patients' self-reported level of education: (1) no education beyond high school, (2) technical school or job training, (3) short-cycle higher education (International Standard Classification of Education level 4, leading to jobs for example dental hygienist), (4) medium-cycle higher education (International Standard Classification of Education level 5, leading to positions such as school teachers or nurse), and (5) long-cycle higher education (International Standard Classification of Education level 5, leading to jobs such as doctor or attorney).²⁴

2.6 | Statistical analysis

We described baseline characteristics with means and standard deviations for continuous, normally distributed variables. Categorical variables were summarized by percentages or frequencies. Comparisons of categorical baseline characteristics between patients and the reference group were performed by Fisher's exact test. The unpaired Student's *t* test was used for normally distributed data. Statistical significance was defined as a *P* value below .05. All analyses were performed using Stata IC 15.1 (StataCorp LP, College Station, TX).

3 | RESULTS

3.1 | Study sample

A total of 2277 patients with a validated diagnosis of ASD, who were 18 years of age or above, comprised the Danish ASD cohort. Information about age and date at diagnosis was available in all patients. The majority, 1554 patients, underwent closure either surgically or by catheter, thereby, leaving a total of 723 patients with an unrepaired ASD. Of these 182 patients were dead and a total of 180 were excluded according to exclusion criteria determined for the main study. Of these, 37 patients (5%) were excluded due to either severe mental or psychiatric disorder incompatible with inclusion for the main descriptive study (Table 1). Finally, 221 patients did not respond to or declined the invitation for the present study leaving 140 patients for participation (Figure 1). Their mean age was 32.6 years, and 60.6% were female.

TABLE 1 Psychiatric diagnoses in patients excluded due to severe mental or psychiatric disorder

	Excluded ASD (n = 34)*
Mental and behavioral disorders due to psychoactive substance use	2
Schizophrenia, schizotypal, and delusional disorders	3
Mood affective disorders	8
Neurotic, stress-related, and somatoform disorders	6
Disorders of adult personality and behavior	2
Mental retardation	12
Disorders of psychological development	8
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	7

*Three patients had more than one diagnosis.

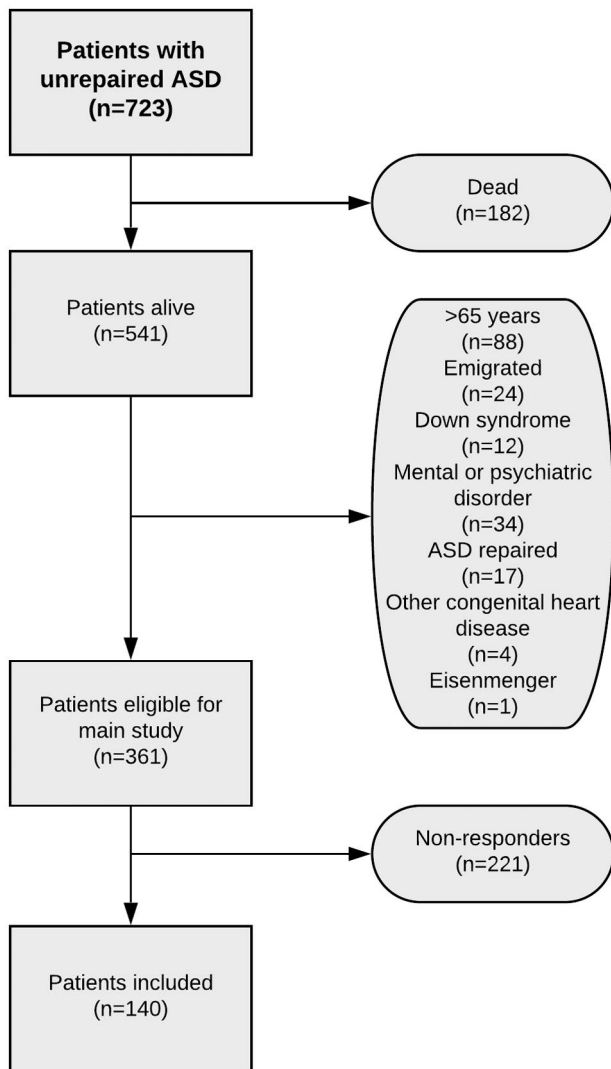


FIGURE 1 Flowchart of patient inclusion

3.2 | Psychiatric diagnoses and register data

A substantial proportion (16.6%) of patients eligible for inclusion had a psychiatric diagnosis (Table 2). Fewer of the participants ($n = 16$, 11.4%) had a psychiatric diagnosis when compared to patients who did not respond to or declined the invitation for the present study ($n = 44$, 19.9%) (Table 2). Additionally, participants were more likely to be younger and female. There were no differences with regard to time of diagnosis, follow-up, or physical comorbidities (chronic lung disease, diabetes, pulmonary heart disease, hypertension, ischemic heart disease, cerebrovascular events, or arrhythmia).

3.3 | Health-related parameters in the study population and in the reference group

Characteristics of the participants are summarized in Table 3. All patients were asymptomatic (in regards to their ASD) at the time of inclusion. With the exception of body mass index (BMI), there were no significant differences in general health parameters (eg, number of daily smokers

TABLE 2 Cohort characteristics and psychiatric diagnoses in included patients and nonresponders

	Included patients $n = 140$	Nonresponders $n = 221$
Female (%)	60.6	38.9
Age (years)	32.6 ± 13	38.7 ± 14
Age at diagnosis (years)	8.8 ± 14	8.9 ± 13
Follow-up (years)	18.9 ± 9	19.2 ± 8
Mental and behavioral disorders due to psychoactive substance use, n (%)	3 (2.1)	4 (1.8)
Schizophrenia, schizotypal, and delusional disorders, n (%)	1 (0.7)	4 (1.8)
Mood affective disorders, n (%)	2 (1.4)	5 (2.2)
Neurotic, stress-related, and somatoform disorders, n (%)	8 (5.7)	19 (8.6)
Disorders of adult personality and behavior, n (%)	0 (0)	9 (4.0)
Mental retardation, n (%)	0 (0)	8 (3.6)
Disorders of psychological development, n (%)	1 (0.7)	5 (2.2)
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence, n (%)	4 (2.8)	11 (5.0)

and drinking habits) between patients and the reference group in the DanFunD study. Notably, a significantly lower proportion of patients with unrepaired ASD rated their mental and physical health as good.

3.4 | Emotional distress

All data from the psychiatric questionnaires and scales are presented in Table 4. All patients' questionnaires were fully completed. A clear pattern was evident regarding depression, somatization, and general anxiety, as patients had significantly higher SCL scores in all categories compared to the DanFunD population. Approximately 7% had a substantial risk (60%) of suffering from anxiety or depression according to SCL-8. However, even though the percentage of patients who scored "high risk" in SCL-8 was greater than the reference group, the difference was not significant. Illness perception and health anxiety scores were comparable between patients and that of the reference group.

3.5 | Educational attainment

One third of patients with unrepaired ASD (33.3%) had no education beyond high school (Table 5). This is a substantial higher percentage

TABLE 3 Comparison of basic characteristics and health related parameters between patients and the reference group

	ASD (n = 140)	DANFUND (n = 1120)	P value
Age (years)	32.6 ± 13	34.2 ± 13	.171
Sex (% female)	60.6	58.0	.366
Height (cm)	172.0 ± 10	172.9 ± 10	.306
Weight (kg)	75.5 ± 19	73.5 ± 15	.161
BMI (kg/m ²)	25.3 ± 5	24.5 ± 4.3	.046
Smoking daily (%)	16.5	12.2	.139
Alcohol (days a week)	1.5 ± 1.1	1.7 ± 1.4	.059
Self-estimated overall health (excellent/good) (%)	87.9	93.5	.022
Self-estimated physical health (good) (%)	22.3	40.0	<.001

when compared to that of the reference group (14.3%; $P < .001$). Additionally, a smaller proportion of patients had completed technical schools, job training, or short-cycle higher educations, whereas the proportion of participants who completed medium- and long-cycle higher education were identical between the two groups.

4 | DISCUSSION

This is the first study to combine register-based data on psychiatric diagnosis with self-reported measures on emotional distress and educational levels in patients with small, unrepaired ASD. Our study shows that even in a quite selected group of these patients, where those with the most severe psychiatric diseases were excluded a priori, a diagnosis of a small ASD still seems to have a substantial impact on their mental well-being and educational attainment. First, 16.6% of these patients had one or more register-based psychiatric

diagnoses. Second, they also as a group had more self-reported symptoms of depression, somatization, and anxiety when compared with the reference group, and thirdly, a significantly higher proportion had no education beyond high school level compared to the reference group.

Patients diagnosed with a small unrepaired ASD were until just recently considered as healthy as the reference group and, despite the ACC/AHA 2008 guidelines suggesting routine follow-up of patients with a small ASD every 2-3 years, most patients are discharged in late adolescence.^{25,26} However, late consequences of living with such a defect, including increased risk of premature death and more chronic diseases, have been demonstrated.⁸ Now, we have documented that the impact of a small ASD has effects beyond physical functioning and, although perhaps interrelated, also impacts on patients' levels of emotional distress. These data are taken as further support for the notion that cognitive and psychiatric issues in ACHD, in particular ASD, patients are a growing concern. Indeed, these issues were recently selected by a NHLBI/ACHA working group as a subject that needs to be prioritized and, subsequently, it has been reported that more than one third of ACHD patients have documentation of depression or anxiety in their medical records.^{10,27} This in accordance with a German study describing an increased prevalence of mood disorders, especially major depressive disorders, and anxiety disorders in ACHD patients when compared to the reference group.³ Interestingly, ASD was the most common congenital malformation among ACHD patients with depression or anxiety, and generally these patients were more likely to have a simple congenital lesion.¹⁰ It seems fair to assume that the size of the defects reported in these above-mentioned studies all were large and significant, which is in contrast to the patients examined in this current study. Therefore, it is noteworthy that even in this selected group of patients with a small ASD a substantial proportion had a psychiatric diagnosis, and more symptoms of depression and anxiety were present, thereby indicating that an ASD, whatever the size, is associated with a psychiatric burden.

Given the more frequent depressive and anxious symptoms compared to that of the reference group, it is perhaps somewhat surprising that symptoms of health anxiety were similar in ASD

TABLE 4 Self-reported mental health in patients compared to the reference group

	Instrument	ASD (n = 140)	DANFUND (n = 1220)	P value
Somatization	SCL-Som	0.51 ± 0.48	0.34 ± 0.39	<.001
Depression	SCL-Dep	0.41 ± 0.56	0.30 ± 0.47	.014
Anxiety	SCL-Anx	0.61 ± 0.70	0.45 ± 0.56	.004
Depression or anxiety	SCL-8	0.57 ± 0.67	0.39 ± 0.52	<.001
Depression or anxiety (high risk)	SCL-8 (dichotomized score ≥5 points)	6.5%	4.1%	.196
Illness perception	BIPQ	27.1 ± 12.0	26.6 ± 10.7	.649
Health anxiety	Whiteley-7	10.3 ± 4.4	10.1 ± 4.1	.702

TABLE 5 Comparison of educational attainment between patients and the reference group

	ASD (n = 140)	DANFUND (n = 1120)	P value
Education level, n (%)			
No education beyond high school (%)	33.3	14.3	<.001
Technical school or job training (%)	28.3	38.7	.020
Short-cycle higher education, 2-3 years (%)	6.5	16.1	.002
Medium-cycle higher education, 3-4 years (%)	19.6	20.6	.825
Long-cycle higher education, >4 years (%)	10.1	10.4	1.000

patients and the reference group. This might support the notion that it is not the diagnosis of ASD itself that makes the patients anxious. Further supportive of this is the fact that all included patients were asymptomatic and none of them were in any follow-up programs. Some patients were not even aware of their ASD diagnosis, as the defect was diagnosed in early childhood. A potential mechanism for the increased emotional distress may be related to right-to-left atrial shunting. A persistent foramen ovale appears more frequent in patients with cerebral ischemia, and microembolization in these patients is related to elevated white matter hyperintensity in patients with Alzheimer's disease.²⁸ However, it remains unknown if these results are inter-related to development of psychiatric disease and whether the results can be extrapolated to patients with ASD. While speculative, another explanation for our findings, as well as the general overrepresentation of depression and anxiety diagnosis in ACHD patients, might originate from factors involved in prenatal neurodevelopment, rather than the contemporary hemodynamic effects of having a congenital lesion. We can only hypothesize whether the abnormalities we found, are a consequence of, for example, genetic predisposition or angiogenic imbalance during pregnancy, as ASD were strongly associated with early preterm preeclampsia (OR: 12.0 [CI: 8.96-16.1]), perhaps affecting the neurodevelopment in the fetal period.²⁹ Additionally, preterm birth might be a contributing factor, as it have been associated with psychiatric disorders.³⁰

Although life expectancy is improved over the last decades, patients with ASD, even if small and unrepaired, continue to have an increased mortality risk compared to the reference group.⁷ Given the fact that depression in ACHD patients is associated with worse survival prospects and increased health care utilization, it might be possible that ASD patients with depression or emotional distress have poorer late outcome than ASD patients without such complaints.^{4,10} Generally, depression increases the risk of death even in individuals without preexisting cardiac disease.³¹ The pathogenic basis for the higher mortality in these patients is uncertain, but it seems that nonsuicide mortality is mostly associated with cardiovascular death, self-harming behavior, and substance abuse.³² As a consequence,

one study suggested that all ACHD patients should be offered a screening at least once for depressive symptoms to improve outcome and avoid preventable complications.⁴ Whereas patients with congenital heart disease in Denmark have a documented excess risk of psychiatric diseases, future research must establish whether adult patients with a small ASD have an increased prevalence of psychiatric diagnoses and prescriptions for psychiatric medicine compared to the reference group, especially depression and anxiety.³³ This would support that these patients require special attention.

As for our other findings, educational levels were lower compared to the reference group. However, the educational attainment could be divided into two, given that the proportion of patients with education beyond high school was lower than the reference group, whereas the proportion of participants who completed medium- and long-cycle higher education were similar. Therefore, our results are both in agreement with and in contrast to a Danish population-based study, showing fewer patients with congenital heart defects completed basic and upper secondary school as well as medium- and long-cycle education.³⁴

As a note, educational levels is found to be independently associated with unemployment in ACHD patients, thereby, perhaps explaining our earlier data, that a lower proportion of patients with a small ASD is employed.³⁵ Our data do not allow for firm conclusions on the mechanism behind the lower educational levels in patients with small ASD; however, an explanation is most likely to be multifunctional.

5 | LIMITATIONS

The current study sample was derived from a patient population where those with severe mental and psychiatric issues were excluded ($n = 34$), since it was anticipated that they would not be able to complete the study protocol in a main study (eg, exercise test and 7-day Holter monitoring). The participants are therefore likely to represent the healthiest patients (regarding a mental illness) with unrepaired ASD. However, since the included patients still had higher levels of emotional distress and lower educational levels, it seems fair to assume that the differences, we found, would only have been greater if the most diseased patients had been included. Further, examining the healthiest patients might also explain why the proportion of patients who scored "high risk" in SCL-8 was insignificantly different compared to the reference group. Also, using a reference group such as the DanFunD study, addressing health-related distress in the public, might not be generalizable to the entire Danish populations or other populations, as the risk of selection bias might influence their results. While speculative, the consequences might be that the assessed variables of emotional distress in our comparison cohort is higher than in the general population. Additionally, we had a relatively low recruitment rate of patients that might reduce the generalizability of the sample; however, the included patient did display similar demographics as ASD patients in general.

Previous data on defect characteristics and shunt dimensions at time of diagnosis was, unfortunately, not always available. Therefore, the identification of a “small defect” is based on the description made by the attending cardiologist at the time of diagnosis, and that the defect was deemed not to undergo closure. That said, our earlier data demonstrated that when we formally reassessed them, only 10 of 153 patients with an unrepaired ASD had defects that warranted intervention on the basis of right ventricular dilation. Not a single patient had an anatomically “large” defect, which reassures us that the label of “small defect” is correct.

Finally, we cannot readily conclude whether the prevalence of psychiatric diagnoses in patients with small, unrepaired ASD are within normal ranges or not, given that the prevalence of psychiatric diagnoses in adults living in Denmark, to our knowledge, is unknown. Further, we used self-reported measures rather than semi-structured clinical interview (gold standard) for diagnosing psychiatric disease, however, this approach was not practically feasible.

6 | CONCLUSION

In this study, patients diagnosed with a small, unrepaired ASD have more symptoms of anxiety, depression and somatization compared to the reference group. Furthermore, fewer patients had no education beyond high school. This might suggest, albeit not examined in the present study, a bidirectional relationship between mental health and educational attainment. These outcomes are despite the fact that the patients with the most severe mental and psychiatric diagnoses were excluded, and, consequently, included patients were considered the healthiest of the entire cohort. These results further support the growing evidence that adults with small ASD warrants regular lifelong follow-up in specialized clinics aware of not only somatic but also adverse psychiatric outcomes, as these patients might have poorer outcome and require special attention.

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CONFLICT OF INTEREST

All authors have no conflicts to disclose.

AUTHOR CONTRIBUTIONS

Construction of idea, planning of research, conduct of research, manuscripting writing, and revision: Udholm, Nyboe, Rask, Hjortdal.

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