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ORIGINAL RESEARCH

Cause-Specific Mortality of Patients With Atrial Septal Defect and Up to 50 Years of Follow-Up

Valtteri Muroke, MD; Mikko Jalanko, MD, PhD; Jari Haukka, PhD; Juha Sinisalo, MD, PhD

BACKGROUND: This study aimed to evaluate the long-term mortality and cause-specific mortality of patients with atrial septal defect (ASD) in a nationwide cohort.

METHODS AND RESULTS: All patients diagnosed with simple ASD in the hospital discharge registry from 1969 to 2019 were included in the study. Complex congenital defects were excluded. Each subject was matched with 5 controls according to sex, age, and municipality at the index time. Adjusted mortality risk ratios (MRRs) were calculated using Poisson regression models. The median follow-up time was 11.1 years. Patients with ASD had higher overall mortality during follow-up, with an adjusted MRR of 1.72 (95% CI, 1.61–1.83). Patients with closed ASDs also had higher total mortality (MRR, 1.29 [95% CI, 1.10–1.51]). However, no difference in mortality was detected if the defect was closed before the age of 30 (MRR, 1.58 [95% CI, 0.90–2.77]), and transcatheter closed defects had lower mortality than the control cohort (MRR, 0.65 [95% CI, 0.42–0.99]). Patients with ASD had significantly more deaths due to congenital malformations (MRR, 54.61 [95% CI, 34.03–87.64]), other diseases of the circulatory system (MRR, 2.90 [95% CI, 2.42–3.49]), stroke (MRR, 1.89 [95% CI, 1.52–2.33]), diseases of the endocrine (MRR, 1.88 [95% CI, 1.10–3.22]) and respiratory system (MRR, 1.71 [95% CI, 1.19–2.45]), ischemic heart disease (MRR, 1.62 [95% CI, 1.41–1.86]), and accidents (MRR, 1.41 [95% CI, 1.05–1.89]).

CONCLUSIONS: Patients with ASD had higher overall mortality compared with a matched general population cohort. Increased cause-specific mortality was seen in congenital malformations, stroke, and heart diseases.

Key Words: congenital ■ congenital heart disease ■ epidemiology ■ heart septal defect ■ mortality

Atrial septal defect (ASD) is a common congenital heart disease, with a birth prevalence of 2.5/1000 live births, 25% to 30% of which present in adulthood.[1,2] ASD allows for left-to-right shunting at the atrial level, promoting right-sided cardiac overload and dysfunction. It also serves as a conduit between systemic and pulmonary circulation and is involved in the mechanism of paradoxical embolism. Patients with ASD have increased mortality, more chronic heart diseases, and strokes.[3–5]

Surgical ASD closure enhances patient survival and long-term safety when performed at a young age.[6] In the 2000s, transcatheter closure has become the primary therapy for many secundum-type ASDs with lower mortality and lower complication rates.[7,8] Transcatheter closure has also been linked to lower mortality than surgical closure.[8]

The most common causes of death for patients with ASD are heart diseases, followed by cancer and infections.[3,9,10] An estimated 30% of the deaths are related to ASD in surgically closed patients.[9]

Although numerous studies have been published on the long-term mortality of ASDs, most have been limited to a small number of outcomes, a small population, or a short follow-up time.[3,10–12] Several studies have reported the causes of death in patients with ASD.[3,9,13] However, large data sets describing cause-specific mortality are lacking.

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CLINICAL PERSPECTIVE

What Is New?

- Patients with atrial septal defect have higher overall mortality compared with a control cohort; however, increased mortality is not seen if the defect is closed before the age of 30.
- Higher mortality is not seen in atrial septal defects closed with the transcatheter approach.
- Increased cause-specific mortality is seen in congenital malformations, stroke, and ischemic heart disease.

What Are the Clinical Implications?

- Patients with atrial septal defect may warrant long-term cardiology follow-up because of their higher cardiovascular mortality.
- Transcatheter atrial septal defect closure should be preferred in eligible patients.

Nonstandard Abbreviations and Acronyms

FHDR	Finnish Hospital Discharge Registry
MRR	mortality risk ratio

This research aimed to determine the long-term mortality of patients with ASD and the mortality of closed defects in a large nationwide cohort of patients with long follow-up. We aimed to report new data on the causes of death in patients with ASD and identify areas that will demand special attention in the long run.

METHODS

Study Setting and Data Source

The data that support the findings of this study are available from Statistics Finland and the FHDR (Finnish Hospital Discharge Register), but restrictions apply to data availability, which were used under license for the current study and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from Statistics Finland and the FHDR.

The research was conducted in Finland, which has a population of approximately 5.5 million people.[14] Finnish health services offer tax-supported health care to all Finnish people.

We gathered the information of all patients diagnosed with ASD from the FHDR (Dnro THL/4814/14.02.00/2020). Primum-type defects were not included in the study. The FHDR is an old, individual-level data register widely used for research purposes. Nationwide hospital discharge data with personal identification numbers have been collected in the register since 1969. Procedural codes were added to the register in 1986. Register coverage is reportedly over 95%, and the positive predictive value for common diagnoses is between 75% and 99%.[15] The validity of many diagnosis codes has been studied previously.[15–17]

The register contains information on admission and discharge dates, surgical procedure codes, and diagnosis codes according to the *International Classification of Diseases* (*ICD*). The *Eighth Revision* of the *ICD* (*ICD-8*) was used until the end of 1986, the *Ninth Revision* (*ICD-9*) from 1987 to 1995, and the *Tenth Revision* (*ICD-10*) thereafter. The *ICD* codes were coded in 2 decimal accuracies. Procedure codes were named according to the Finnish hospital alliance codes until 1995 and according to the Nordic Classification of surgical procedures after that.

All patients with *ICD-8*, *ICD-9*, or *ICD-10* codes for ASD, except for primum defects, were included (Table S1). Patients with *ICD-8*, *ICD-9*, or *ICD-10* codes for more severe congenital heart disease were excluded, except codes not specific to congenital heart disease (747.7–747.9 [*ICD-8*], 7474x–7479x [*ICD-9*], and Q26.5–Q26.6 [*ICD-10*]). Out of all congenital heart diseases, only the patent arterial duct was considered a less severe defect. All the included patients had relevant data elements available, and no patients were excluded because of the missing data.

For every patient with ASD, 5 individually matched controls from the general population were matched to birth year, residence (city or municipality) at the index date, and sex. The index date was defined as the date of closure and date of diagnosis for patients with unclosed ASD. Controls were excluded if they had diagnosis of ASD.

Data on deaths were obtained from Statistics Finland. Both underlying and immediate causes of death were coded using *ICD*. In addition, a cause of death classification with 54 categories was used.[18]

Statistical Analysis

Mortality risk ratios (MRR) were adjusted for sex, age, year at the start of follow-up, and age at the start of the Lexis period. Interactions between confounders and the main exposure in the final model can be found in the Table S2. Comorbidity was indexed using the Charlson comorbidity index, which includes diagnoses for diabetes, malignancies, human immuno deficiency virus, and cerebral, heart, liver, lung, and renal diseases.[19,20] Conditions that could have been a direct consequence of ASD, such as cerebrovascular disease and hemiparesis, were excluded from the index. Comorbidities were tested in the model using nested case–control analysis. The nested case–control analysis included 5 controls still under observation for each case with an outcome. Comorbidity indexing did not have a notable impact on

the results and was not included in the main analysis. Down syndrome was also examined in the model, but it had no discernible effect on the outcome and was not included in the main analysis (Table S3). The comorbidity-adjusted odds ratios are shown in Tables S4 and S5.

Follow-up began from the time of diagnosis and continued until death or the end of follow-up (December 31, 2019). Kaplan–Meier estimates were calculated from the time of diagnosis. We modeled mortality using Poisson regression models with a Lexis-type data structure with 3 time scales: age, calendar year, and time since diagnosis.[21] Poisson regression with 95% CIs was used to calculate MRRs. The duration was offset in the Poisson analysis. The Shapiro–Wilk test was used to determine the normality of baseline variables. The chi-square test or Mann–Whitney *U*-test was used to compare baseline characteristics. All analyses were performed using R software, version 4.2.1.

Ethics

The Helsinki university hospitals ethics committee approved this study on November 7, 2019 (num. HUS/1820/2019), and it was conducted following the Declaration of Helsinki. Patient consent was not needed for register-based research.

RESULTS

Study Cohort

A total of 14 331 patients had a diagnosis code for ASD or a procedural code for ASD closure in the FHDR between 1969 and 2019. After exclusion, a total of 9084 patients were included in the study (Figure 1). The rate of ASD diagnoses began increasing between 1990 and 2000. Consequently, the majority (71.1%) had start of the follow-up in the 2000s (Figure 2). The median follow-up was 11.1 years (range, 0–51 years). The number of patients in different birth cohorts is described in Table 1. Follow-up data were available for 9017 (99.3%) patients, resulting in 131 003 patient-years.

Patients with ASD had more baseline comorbidities at the time of diagnosis than the control group (Table 1). ASD closure was performed for 2281 patients from 1986 to 2019 at the mean age of 30.8 years (range, 0–84 years). Of these patients, 1472 had surgical closure, and 856 had transcatheter closure. All the surgical and transcatheter closures were performed at Finland's 5 university hospitals.

Mortality

Patients with ASD had higher overall mortality, with an adjusted MRR of 1.72 (95% CI, 1.61–1.83). MRRs were 1.79 (95% CI, 1.65–1.94) for female patients and 1.64 (95% CI, 1.48–1.81) for male patients. Female patients with ASD had lower mortality compared with male counterparts (MRR, 0.66 [95% CI, 0.59–0.74]). This mortality difference was also seen in the control population (MRR, 0.61 [95% CI, 0.58–0.65]). Mortality in different birth cohorts is shown in Figure S1.

Patients with closed ASDs had higher total mortality (MRR, 1.29 [95% CI, 1.10–1.51]) (Figure 3). No difference in mortality was detected if the defect was closed before the age of 30 (MRR, 1.58 [95% CI, 0.90–2.77])

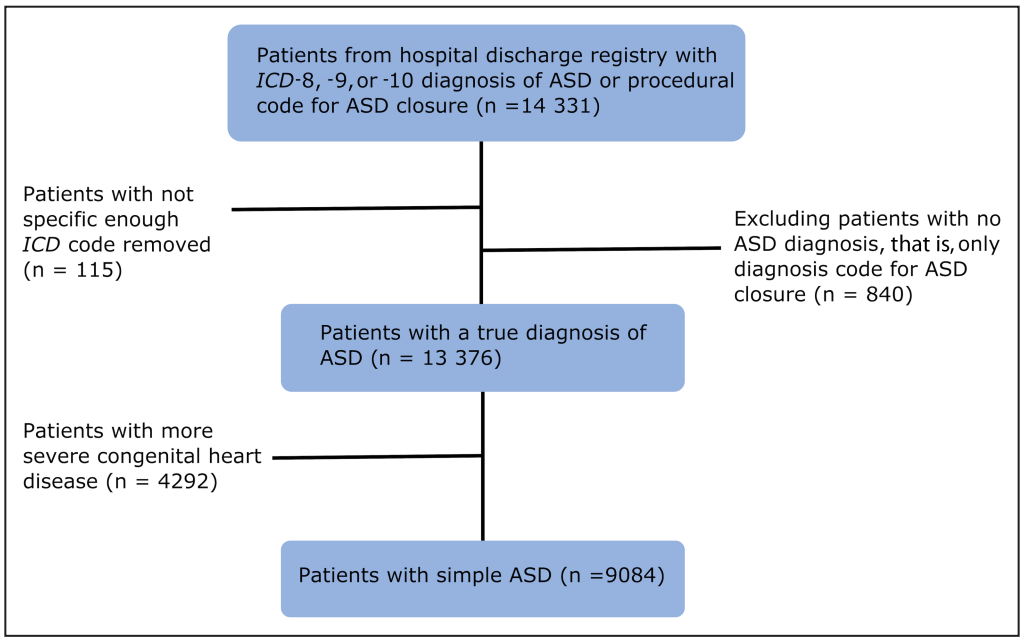

Figure 1. Patient selection flow chart.
ASD indicates atrial septal defect; and *ICD*, *International Classification of Diseases*.

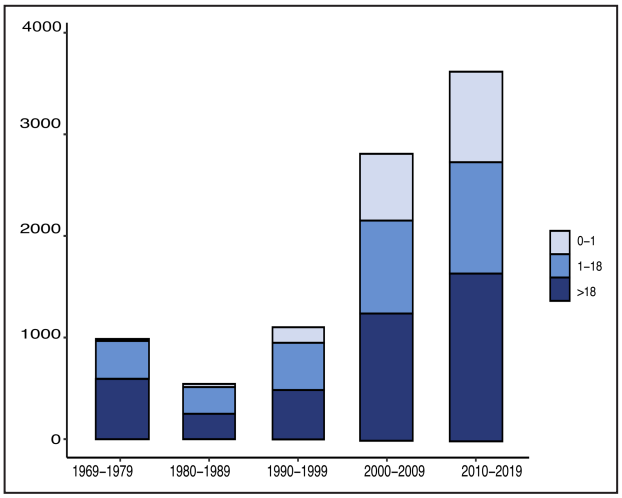

Figure 2. Patient age and the decade at the start of follow-up. Bars are divided according to different age groups. Age refers to the age at the start of follow-up.

(Figure S2). In surgically closed defects, the MRR was 1.49 (95% CI, 1.26–1.76) (Figure 4).

Table 1. Baseline Characteristics at the Time of Diagnosis

Characteristic	ASD group (n=9084)	Control group (n=43341)	*P* value
Age at the start of follow-up, y	26.0 (26.2)	25.6 (26.4)	0.20
Median follow-up (interquartile range)	11.1 (5.1–19.4)	11.4 (5.5–19.3)	0.04*
Female sex	60.5 (5492)	60.1 (26068)	0.59
Birth year			
2000–2019	32.4 (2941)	33.7 (14606)	0.001*
1980–1999	19.1 (1735)	19.9 (8629)	
1960–1979	16.4 (1488)	16.4 (7102)	
1940–1959	19.3 (1757)	17.6 (7642)	
1920–1939	11.3 (1025)	11.0 (4746)	
Before 1920	1.5 (138)	1.4 (616)	
Age at the time of death, y	67.0 (21.3)	75.2 (15.6)	<0.001*
Hypertension	7.0 (639)	3.7 (1620)	<0.001*
Atrial fibrillation	8.6 (785)	1.4 (626)	<0.001*
Pulmonary hypertension	0.8 (68)	0.02 (9)	<0.001*
Diabetes	2.6 (240)	1.8 (772)	<0.001*
Ischemic heart disease	5.8 (529)	2.8 (1200)	<0.001*
Stroke	6.2 (563)	1.1 (492)	<0.001*
Down syndrome	2.9 (265)	0.06 (26)	<0.001*
Type of defect			
Secundum	62.2 (5646)		
Sinus venosus	0.9 (78)		
Unroofed coronary sinus	0.08 (7)		
Undetermined	36.9 (3353)		

Values are presented as mean (SD) or percentage (number of patients).
ASD indicates atrial septal defect.
*Indicates statistcally significant difference.

Patients with transcatheter-closed defects had lower mortality than the control cohort (MRR, 0.65 [95% CI, 0.42–0.99]). Lower mortality was also seen when compared with surgically closed defects (MRR, 0.37 [95% CI, 0.23–0.59]) (Figure 3).

There were in total 1271 deaths in the ASD population (Table 2). A total of 98 deaths had occurred in the patient group by the age of 30 and 202 deaths by the age of 50. This equated to a cumulative mortality risk of 1.1% at 30 years of age and 2.2% at 50 years. The comparable cumulative mortality risks were 0.2% and 0.7% in the control cohort, respectively.

The 30-day mortality after closure was 0.2% (n=5), each incident of which occurred after surgical closure. One of the patients died at the age of 8 years. The cause of death of 2 patients was a secundum-type ASD. The other 3 died of ischemic heart disease.

Cause-Specific Mortality

Ischemic heart disease (20%, n=251), congenital malformations (15.2%, n=193), and neoplasms (12.4%, n=158) were the most common causes of death in patients with ASD. Congenital malformations are defined as any *ICD* code for congenital malformation that could have been logically implicated as the root cause of death. The defect itself was the cause of death in 7.5% (n=95) of patients with ASD.

Compared with the controls, patients with ASD experienced significantly more deaths due to any kind of congenital malformation (MRR, 54.61 [95% CI, 34.03–87.64]), other diseases of the circulatory system (MRR, 2.90 [95% CI, 2.42–3.49]), stroke (MRR, 1.89 [95% CI, 1.52–2.33]), diseases of the endocrine (MRR, 1.88 [95% CI, 1.10–3.22]) and respiratory systems (MRR, 1.71 [95% CI, 1.19–2.45]), ischemic heart disease (MRR, 1.62 [95% CI, 1.41–1.86]), and accidents (MRR, 1.41 [95% CI, 1.05–1.89]) (Figure 5).

Risk of death from other heart diseases was most pronounced in valvular diseases (MRR, 5.65 [95% CI, 3.89–8.21]), cardiomyopathies (MRR, 3.77 [95% CI, 2.286.23]), and rhythm disturbances (MRR, 3.19 [95% CI, 1.43–7.11]). The adjusted MRR for having heart failure as the immediate cause of death was 4.99 (95% CI, 3.90–6.40). Total cardiovascular mortality is shown in Figure 3.

We observed no difference in neoplasm (MRR, 1.01 [95% CI, 0.86–1.18]), dementia (MRR, 0.92 [95% CI, 0.73–1.18]), central nervous system disease (MRR, 1.46 95% [CI, 0.96–2.22]), infectious disease (MRR, 1.32 [95% CI, 0.82–2.12]), suicide (MRR, 1.20 [95% CI, 0.76–1.89]), or alcohol-related mortality (MRR, 1.13 [95% CI, 0.76–1.68]).

DISCUSSION

This study is the most extensive nationwide cohort describing mortality and causes of death in patients

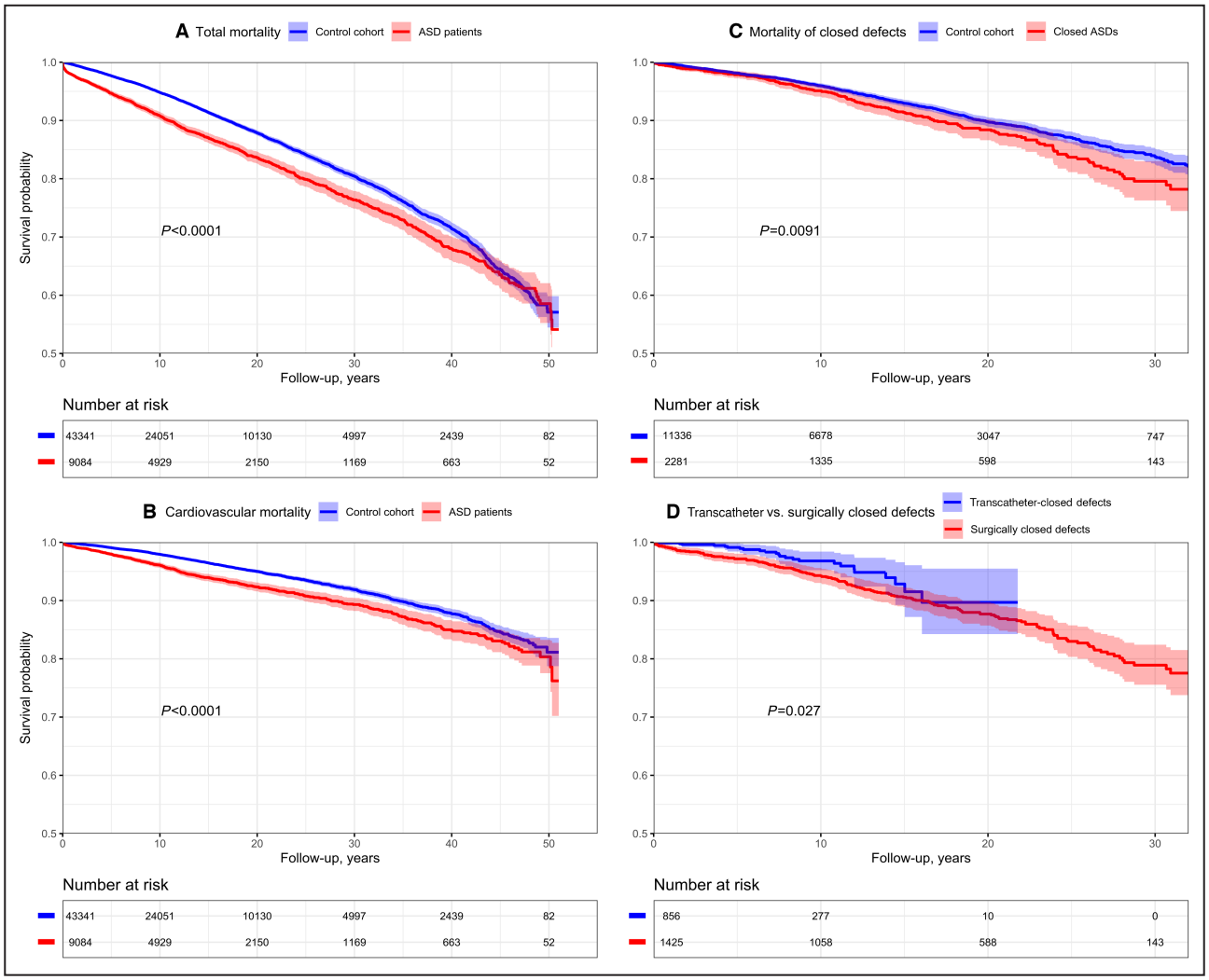

Figure 3. Kaplan–Meier estimates of mortality.
Long-term mortality according to study groups. **A**, Total mortality, (**B**), cardiovascular mortality, (**C**), mortality of closed atrial septal defects compared with the control population, (**D**), mortality of transcatheter and surgically closed patients. Only individualized controls were included in the analysis. Mortality risk ratios are adjusted to sex, age, year at the start of follow-up, and age at the beginning of follow-up. ASD indicates atrial septal defect; and TC, transcatheter.

with ASD and long follow-up times. It shows that the mortality of patients with ASD is higher compared with the background population. The follow-up in our study can be considered nearly complete, as only emigrated patients are lost to follow-up.

Similar increases in mortality were also seen in previous studies.[3,22] The increase in mortality was similar in male and female groups in contrast to a Dutch study, which found increased mortality only in the male population with ASD.[10]

Cause-Specific Mortality

Increased mortality was seen mainly because of heart diseases and congenital malformations. Stroke and heart failure can be considered a direct consequence of ASD, and valvular diseases may result from volume overload caused by ASD. However, there is no explicit mechanism for the increased mortality due to ischemic heart diseases. This finding can only be speculated. In our study patients with ASD had more risk factors like diabetes and hypertension for coronary artery disease, which could explain the higher mortality in ischemic heart diseases. To our knowledge, increased mortality in patients with ASD due to ischemic heart diseases has not been published previously. We did not find any apparent reason for the increased mortality due to endocrine and respiratory diseases or accidents, but competing causes of death may have contributed to this finding.

ASD was the cause of death in 7.5% of the patients. Immediate cause of death information was available for

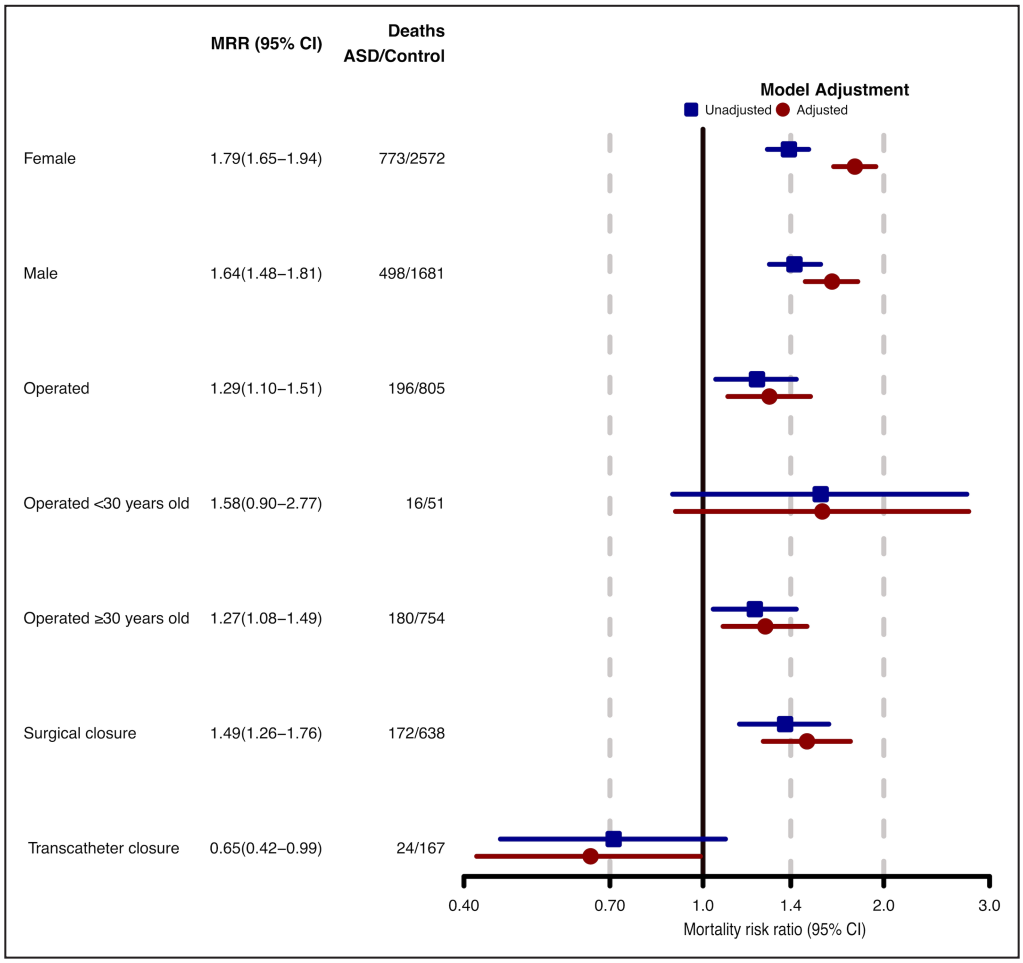

Figure 4. Mortality risk ratios in different ASD groups compared with the control population. Mortality risk ratios are adjusted to sex, age, year at the start of follow-up, and age at the beginning of follow-up. ASD indicates atrial septal defect; and MRR, mortality risk ratio.

68% of these patients, with heart failure as the immediate cause of death in 46% of patients, and ASD was deemed the cause of the failing heart. In the Danish cohort, 14% to 15% of patients had ASD as the cause of death.[3]

Closed Defects

We found that, overall, closed ASDs had higher mortality compared with the controls. Excess mortality was not seen if the ASD was closed before 30 years of age.

Interestingly, mortality was lower in percutaneously closed defects. This finding has not been reported previously. Previously, long-term mortality has been reported to be similar between percutaneously closed defects and matched control populations.[13,23]

This low mortality may be explained by selection. Patients with advanced diseases and poor prognoses are often left untreated. In addition, patients with ASD and pulmonary vascular resistance ≥5 Woods units are not closed. Low mortality may also be influenced by the fact that only small to moderate-sized, centrally located defects are suitable for catheter closure, and transcatheter-closed defects tend to be hemodynamically less severe.[24] Lower mortality of transcatheter-closed defects compared with the surgically closed ones (MRR, 0.37) is also at least partly explained by the aforementioned patient selection and indication bias.

Murphy et al reported similar findings on surgically closed patients in 1990.[6] They found that patients with ASD did not have increased mortality if the defect was closed before the age of 25. Patients in that study were operated on between 1956 and 1960. Similarly, an excellent long-term prognosis has been reported in a Dutch study that included <15-year-old patients operated on between 1969 and 1980.[25] In our cohort of operated patients, the operations were performed between 1986 and 2019.

Table 2. Number of Deaths and All-Cause Mortality Rates (per 1000 Person-Years) for Baseline Characteristics

		ASD			Control			
	Group	Pyears	Event	Rate (95% CI)	Pyears	Event	Rate (95% CI)	MRR (95% CI)
Sex	Male	50.31	498	9.90 (9.05–10.81)	242.64	1681	6.93 (6.60–7.27)	1.43 (1.29–1.57)
	Female	80.70	773	9.58 (8.92–10.28)	375.10	2572	6.86 (6.59–7.13)	1.39 (1.28–1.51)
Age at the SOF, y	<30	91.04	188	2.07 (1.78–2.38)	411.18	324	0.79 (0.70–0.88)	2.62 (2.19–3.14)
	30–60	29.85	452	15.14 (13.78–16.60)	146.65	1514	10.32 (9.81–10.86)	1.47 (1.32–1.63)
	>60	10.11	631	62.41 (57.63–67.47)	59.90	2415	40.32 (38.72–41.96)	1.55 (1.42–1.69)
Year at the SOF	<1980	36.49	365	10.00 (9.00–11.08)	131.08	1168	8.91 (8.41–9.44)	1.12 (0.99–1.26)
	1980–2000	38.03	400	10.52 (9.51–11.60)	201.88	1409	6.98 (6.62–7.35)	1.51 (1.35–1.68)
	>2001	56.48	506	8.96 (8.20–9.77)	284.77	1676	5.89 (5.61–6.17)	1.52 (1.38–1.68)
Hypertension	no	126.45	1084	8.57 (8.07–9.10)	607.17	3746	6.17 (5.97–6.37)	1.39 (1.30–1.49)
	yes	4.55	187	41.11 (35.43–47.44)	10.57	507	47.97 (43.89–52.34)	0.86 (0.72–1.01)
Atrial fibrillation	no	125.34	985	7.86 (7.38–8.37)	613.93	4020	6.55 (6.35–6.75)	1.20 (1.12–1.29)
	yes	5.67	286	50.47 (44.79–56.67)	3.81	233	61.20 (53.60–69.59)	0.82 (0.69–0.98)
Pulmonary hypertension	no	130.62	1246	9.54 (9.02–10.08)	617.63	4251	6.88 (6.68–7.09)	1.39 (1.30–1.48)
	yes	0.38	25	65.13 (42.15–96.15)	0.10	<5	19.37 (2.35–69.96)	3.36 (0.80–14.20)
Diabetes	no	129.37	1164	9.00 (8.49–9.53)	611.80	3993	6.53 (6.33–6.73)	1.38 (1.29–1.47)
	yes	1.63	107	65.55 (53.72–79.21)	5.94	260	43.80 (38.64–49.46)	1.50 (1.19–1.87)
Ischemic heart disease	no	126.67	1031	8.14 (7.65–8.65)	608.37	3745	6.16 (5.96–6.36)	1.02 (0.88–1.19)
	yes	4.33	240	55.44 (48.65–62.92)	9.36	508	54.26 (49.64–59.19)	8.81 (8.03–9.67)
Stroke	no	126.88	1173	9.25 (8.72–9.79)	614.47	4054	6.60 (6.40–6.80)	1.40 (1.31–1.50)
	yes	4.12	98	23.76 (19.29–28.96)	3.26	199	60.97 (52.79–70.05)	0.39 (0.31–0.50)
Down syndrome	no	128.80	1257	9.76 (9.23–10.31)	617.56	4251	6.88 (6.68–7.09)	1.42 (1.33–1.51)
	yes	2.20	14	6.36 (3.48–10.68)	0.17	<5	11.52 (1.40–41.60)	0.55 (0.13–2.43)

Reported risk ratios are crude risk ratios. CIs are calculated using exact method.
ASD indicates atrial septal defect; MRR, mortality risk ratio; Pyears, Person years; SOF, start of the follow-up.

A nationwide Danish cohort study by Nyboe et al reported that mortality was not higher if the defect was closed before 18 years of age.[3] They did not report data separately for percutaneously and surgically closed defects.

The low 30-day mortality after closure is in concordance with previous studies.[3,26–28] The 30-day mortality after catheter closure was 0%, emphasizing procedural safety.

Limitations

This study was limited by the retrospective nature of its design. Despite the FHDR reportedly being accurate, the possibility of coding misclassifications cannot be completely excluded.

There is some selection bias in patients born before 1969, as patients with more severe defects may have died before the start of follow-up. For patients born before 1969 (n=3739, 41.1% of the study population), the date of diagnosis cannot be known for sure. Follow-up began with the first time that the diagnosis appeared in the FHDR. In patients born before 1969, this could mean the date of diagnosis or a follow-up visit.

The closure rate for patients with ASD in the whole cohort is unknown, as procedural codes were included in the discharge registry only after 1986. Information about the ASD subtypes was limited because *ICD-8* and *ICD-9* (used from 1969 to 1995) were not specific enough to describe various types of ASD. Thus 36.9% of defects were labeled as undetermined.

CONCLUSIONS

Patients with ASD had higher overall mortality compared with a matched general population cohort. Higher cause-specific mortality was seen in congenital malformations, stroke, and heart diseases. Patients

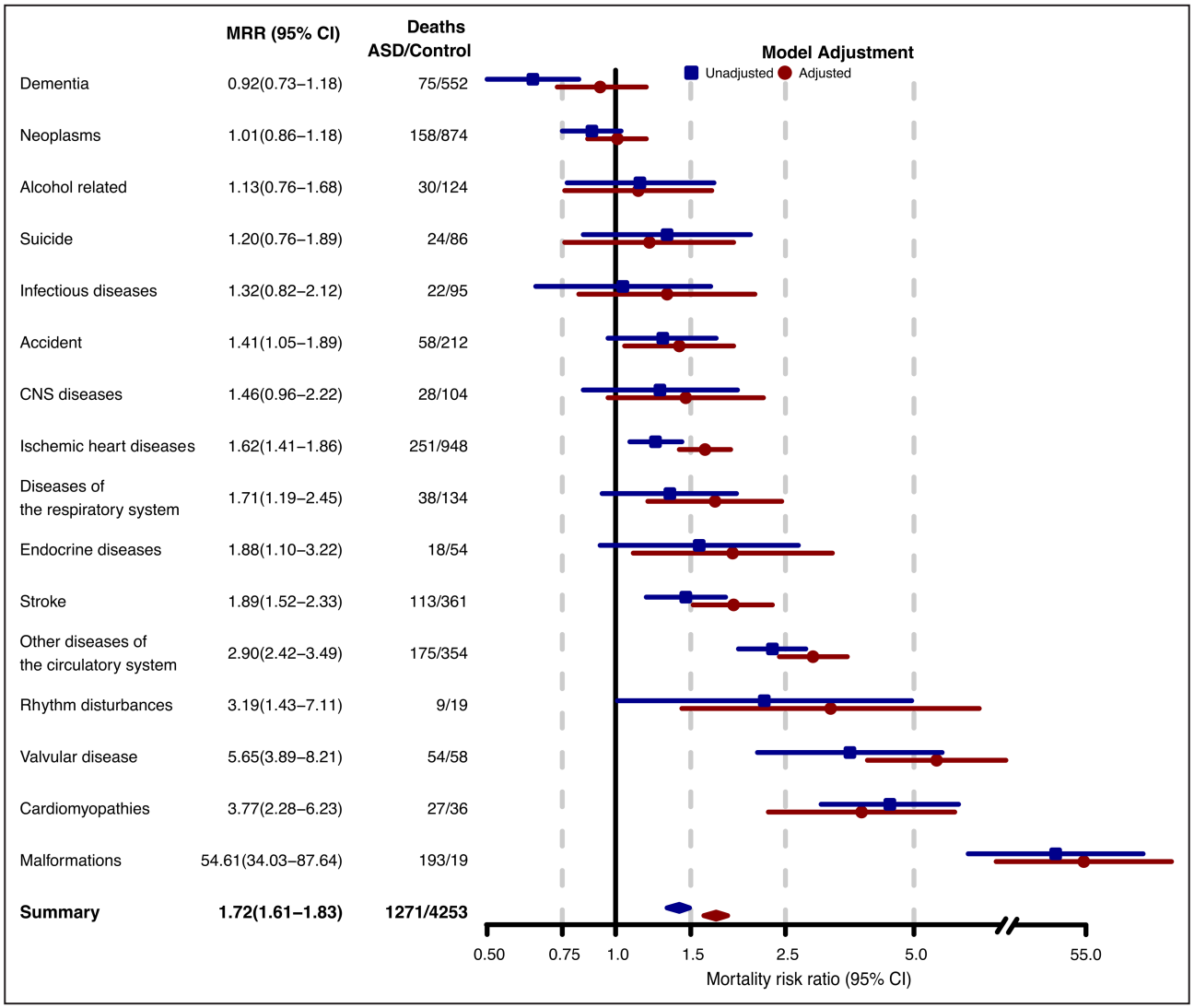

Figure 5. Cause-specific mortality risk ratios of patients with ASD compared with the control population.
Mortality risk ratios are calculated using Poisson regression and adjusted to sex, age, year at the start of follow-up, and age at the beginning of follow-up. ASD indicates atrial septal defect; CNS, central nervous system; and MRR, mortality risk ratio.

applicable for transcatheter closure have an excellent prognosis.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1–S5
Figure S1–S2

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Supplemental Material

Table S1. ICD codes used to define atrial septal defect and procedural codes for defect closure. ICD = International classification of diseases, NCSP = Nordic classification of surgical procedures.

ICD-10	ICD-9	ICD-8	NCSP	Finnish hospital Alliance codes
Q21.10	7455A	746,42	FFC00	5205
Q21.12	7458X	746,43	FFC02	
Q21.13	7459X		FFC03	
Q21.14			FFC22	
Q21.15			FFC50	
Q21.18			FFC96	
Q21.19			FFC00	

Table S2. **Interactions between confounders and main exposure in final model**

Interaction	Mortality risk ratio	95% CI	P-value (Interaction between confounder and main exposure in the final model)
Sex:Age	1.73	1.62-1.84	<0.001
Sex:Age.diagnosis	1.72	1.61-1.83	<0.001
Sex:SOF	1.72	1.61-1.83	<0.001
Age:Age.diagnosis	1.72	1.61-1.83	<0.001
Age:SOF	1.71	1.60-1.82	<0.001
Age.dgn:SOF	1.72	1.61-1.83	<0.001

SOF = start of the follow-up

Table S3. Mortality odds ratios in different models.

Model 1 →Adjusted risk ratio for Sex
Model 2 → Adjusted risk ratio for Sex + Age
Model 3 → Adjusted risk ratio for Sex + Age + Age at the time of diagnosis
Model 4 → Adjusted risk ratio for Sex + Age + Age at the time of diagnosis + Start of follow up
Model 5 → Adjusted risk ratio for Sex + Age + Age at the time of diagnosis + Start of follow up + Down syndrome

	Mortality risk ratio	Model 1	Model 2	Model 3	Model 4	Model 5
Total	1.40(1.32-1.49)	1.40(1.32-1.49)	1.69 (1.59-1.80)	1.70 (1.59-1.81)	1.72 (1.61-1.83)	1.72 (1.62-1.83)
Infectious disease	1.04 (0.65-1.67)	1.04 (0.65-1.67)	1.27 (0.79 – 2.04)	1.27 (0.79 – 2.04)	1.32 (0.82– 2.12)	1.32 (0.82– 2.12)
Neoplasms	0.88(0.75-1.03)	0.88 (0.75-1.03)	1.01 (0.86 – 1.18)	1.01 (0.86 – 1.18)	1.01 (0.86 – 1.18)	1.01 (0.86 – 1.18)
Dementia	0.64 (0.50-0.82)	0.64 (0.50-0.81)	0.91(0.72-1.16)	0.91(0.72-1.16)	0.92 (0.73-1.18)	0.92 (0.73-1.18)
Endocrine diseases	1.57 (0.92-2.68)	1.56 (0.92-2.67)	1.83 (1.07-3.13)	1.84 (1.08-3.14)	1.88 (1.10-3.22)	1.88 (1.10-3.22)
CNS diseases	1.27 (0.84-1.93)	1.27 (0.84-1.92)	1.45 (0.95-2.20)	1.45 (0.95-2.20)	1.46 (0.96-2.22)	1.46 (0.96-2.22)
Stroke	1.46(1.18-1.81)	1.46(1.18-1.80)	1.83 (1.48-2.27)	1.84 (1.49-2.28)	1.89 (1.52-2.33)	1.89 (1.52-2.33)
Ischemic heart disease	1.24(1.08-1.43)	1.25 (1.08-1.43)	1.57 (1.36-1.80)	1.57 (1.37-1.81)	1.62 (1.41-1.86)	1.62 (1.41-1.86)

Other diseases of the circulatory system	2.33 (1.94-2.79)	2.33 (1.95-2.79)	2.89 (2.41-3.47)	2.88 (2.40-3.46)	2.90 (2.42-3.49)	2.90 (2.42-3.48)
Diseases of the Respiratory system	1.34 (0.93-1.92)	1.35 (0.94-1.93)	1.65 (1.15-2.37)	1.66 (1.16-2.38)	1.71 (1.19-2.45)	1.71 (1.19-2.45)
Malformations	46.91 (29.27-75.18)	46.84 (29.22-75.07)	52.33 (32.63-83.92)	52.53 (32.75-84.24)	54.61 (34.03-87.64)	69.61 (41.10-117.89)
Malformations excluding ASD	40.7 (25.31-65.45)	40.64 (25.27-65.35)	45.38 (28.20-73.02)	45.55 (28.31-73.29)	46.62 (28.95-75.6)	59.45 (34.99-100.99)
Accidents and violence	1.29 (0.96-1.72)	1.30 (0.97-1.73)	1.41 (1.05-1.88)	1.40 (1.05-1.88)	1.41 (1.05-1.89)	1.41 (1.05-1.88)
Suicides	1.32(0.84-2.07)	1.33 (0.84-2.09)	1.28 (0.81-2.01)	1.27 (0.81-2.00)	1.20 (0.76-1.89)	1.20 (0.76-1.89)
Alcohol-related diseases	1.14 (0.77-1.70)	1.15 (0.77-1.72)	1.13 (0.76-1.69)	1.14 (0.76-1.70)	1.13 (0.76-1.68)	1.13 (0.76-1.68)
Rhythm disturbances	2.23 (1.01-4.94)	2.22 (1.00-4.90)	3.06 (1.38-6.79)	3.06 (1.38-6.78)	3.19(1.43-7.11)	3.19(1.43-7.11)
Valve disease	4.39 (3.03-6.36)	4.38 (3.03-6.35)	5.60 (3.86-8.12)	5.59 (3.85-8.12)	5.65(3.89-8.21)	5.65(3.89-8.21)

Cardiomyopathies	3.54 (2.15-5.82)	3.57 (2.17-5.87)	3.80 (2.30-6.26)	3.76 (2.28-6.20)	3.77(2.28-6.23)	3.77(2.28-6.23)

Table S4. Mortality odds ratios adjusted for comorbidity. Adjusted for sex + Age + Age at the time of diagnosis + Start of follow up + Charlson comorbidity index using nested case control setting.

	Adjusted Mortality odds ratio
Total	1.60 (1.46-1.75)
Infectious disease	1.26 (0.63-2.50)
Neoplasms	0.95(0.77-1.16)
Dementia	0.99(0.71-1.39)
Endocrine diseases	1.65(0.76-3.59)
CNS diseases	0.91 (0.46-1.79)
Stroke	2.18 (1.60-2.99)
Ischemic heart disease	1.63 (1.35-1.98)
Other diseases of the circulatory system	3.12 (2.34-4.15)
Diseases of the Respiratory system	1.66(1.03-2.68)
Malformations	115.65 (35.41-377.73)
Malformations excluding ASD	60.02 (22.86-157.60)
Accidents and violence	1.50 (0.87 – 2.60)
Suicides	1.64 (0.40 – 6.82)
Alcohol-related diseases	1.59 (0.84-3.03)
Rhythm disturbances	4.22 (1.04 – 17.10)
Valvular disease	6.22 (3.34 - 11.59)
Cardiomyopathies	5.92 (2.19 – 16.09)

Table S5. **Propensity matched Mortality risk ratio analysis Matched for age, age at the time of diagnosis, start of the follow-up date and Charlsons comorbidity index. R MatchIt package used, method = "nearest".**

	Adjusted Mortality odds ratio
Overall mortality	1.37 (1.29-1.46)

Figure S1. Mortality by birth cohorts.

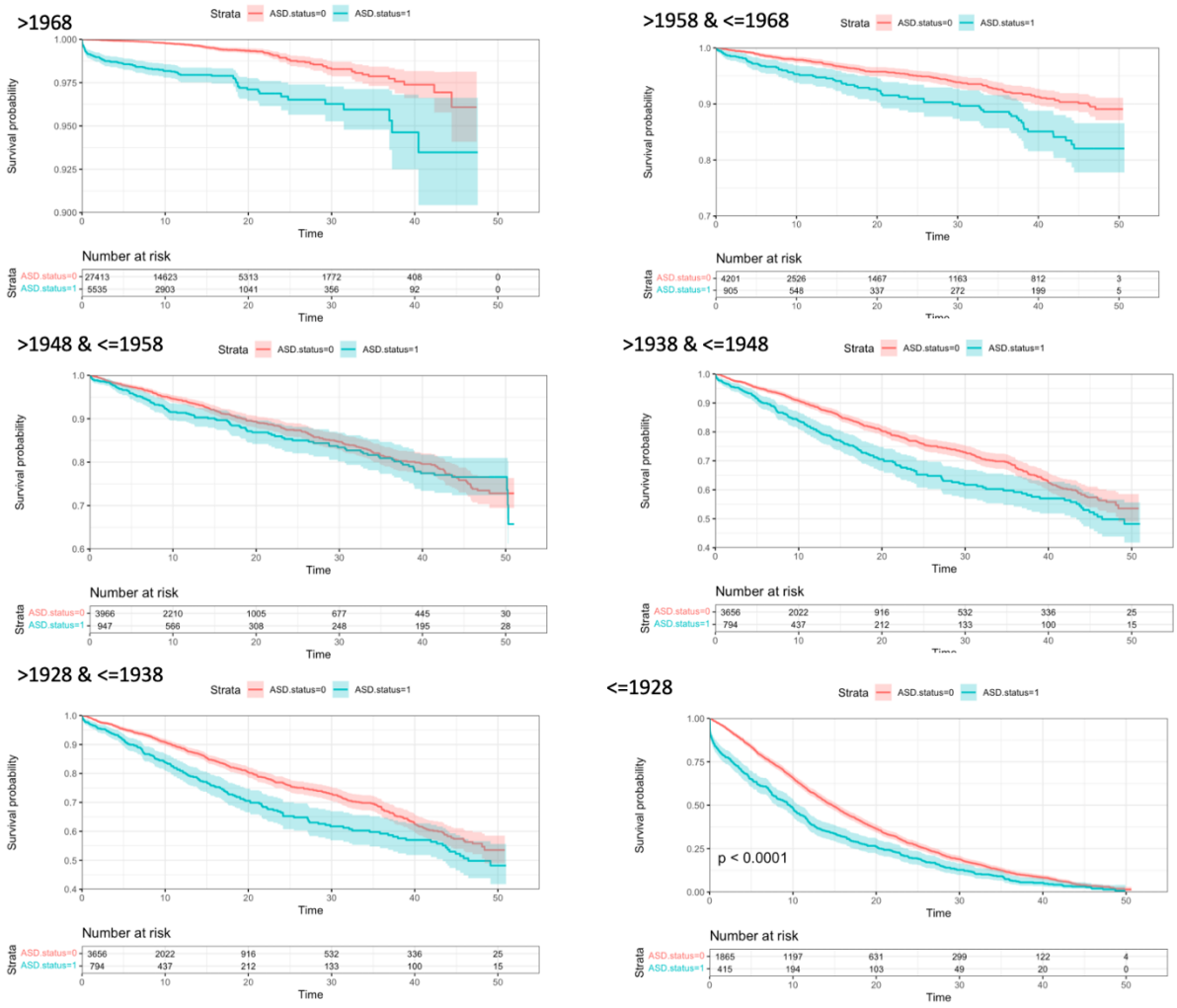
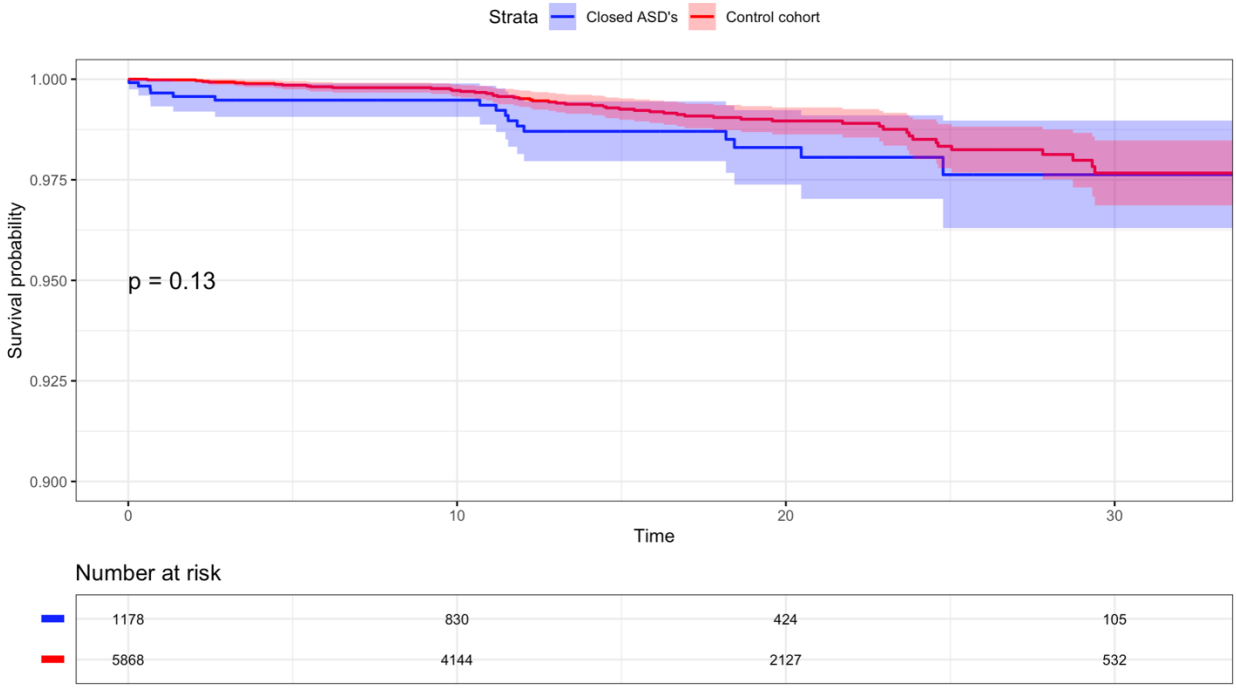


Figure S2.

A) Closure before the age of 30



B) Closure at the age of 30 or older.