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Mortality and causes of death in autism spectrum disorders

An update

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ABSTRACT This study compared mortality among Danish citizens with autism spectrum disorders (ASDs) with that of the general population. A clinical cohort of 341 Danish individuals with variants of ASD, previously followed over the period 1960–93, now on average 43 years of age, were updated with respect to mortality and causes of death. Standardized mortality ratios (SMRs) were calculated for various times after diagnosis. In all, 26 persons with ASD had died, whereas the expected number of deaths was 13.5. Thus the mortality risk among those with ASD was nearly twice that of the general population. The SMR was particularly high in females. The excess mortality risk has remained unchanged since our first study in 1993. Eight of the 26 deaths were associated with epilepsy and four died from epilepsy. Future staff education should focus on better managing of the complex relationships between ASD and physical illness to prevent avoidable deaths.

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Long-term follow-up studies of mixed groups of children and adolescents with psychiatric disorders have found above-average mortality rates compared to age- and sex-matched controls, especially concerning death from 'unnatural causes', i.e. suicide, accident, etc. (de Chateau 1990; Kjeldsberg and Dahl, 1998; Kuperman et al., 1988; Larsen et al., 1990; Ostman, 1991; Rydelius, 1984; Thomsen, 1996).

Mortality information that includes causes of death is important as it can influence care and treatment strategies (Howlin, 2005).

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Only two studies dealing with standardized mortality and causes of death in individuals with autism spectrum disorders (ASDs) have been published so far (Isager et al., 1999; Shavelle et al., 2001). The study of Shavelle et al. (2001) included younger ambulatory age groups from the California developmental disabilities registry. The overall SMR was 2.4. To confirm these results, Pickett et al. (2006) recently updated the Shavelle et al. (2001) study and analysed data for a more recent 5 year span, 1998–2002. As before, excess mortality was observed. An overall SMR of 2.6 for 1998–2002, compared with 2.4 in the 1983–97 period, indicated a mortality rate more than twice as high as that for the general population. In a Danish study (Isager et al., 1999), an overall SMR of 1.9 was reported in a nationally ascertained sample of 341 patients with different variants of ASD, studied over the 1960–93 period.

Occasional deaths have been reported too in general follow-up studies of individuals with ASD (Ballaban-Gil et al., 1996; Billstedt et al., 2005; Fombonne et al., 1989; Howlin et al., 2004; Kobayashi et al., 1992; Larsen and Mouridsen, 1997). Deaths reported in the studies mentioned have resulted from a range of different natural (i.e. pneumonia, status epilepticus) and unnatural causes (i.e. car accidents, drowning, suffocation). ASD individuals with a severe learning disability or epilepsy may be at particular risk (Shavelle et al., 2001), but many other factors are operating and may reduce life expectancy in ASD.

The purpose of the current study was to update our previous study (Isager et al., 1999) and to evaluate whether the increased risk of death among persons with ASD had changed since 1993. The longer follow-up period enabled us to examine the risk of and causes of death among persons with ASD in middle adult life up to 45 years after diagnosis.

Subjects

The study included all patients (age 2–17 years) with variants of ASD originally seen as inpatients at the University Clinics of Child Psychiatry of Copenhagen and Aarhus during the 25 year period 1960–84. Together the two clinics provided services to all Danes. The patients were born in the period 1945–80. Based on the hospital records, all patients were rediagnosed in 1985 by BR and SEM. Diagnosis was based on criteria applicable at the time the children were rediagnosed in 1985, i.e. mostly ICD-9 (World Health Organization, 1978). Although classification systems have been modified since then, the core ASD criteria currently used in ICD-10 (World Health Organization, 1992) remain similar to those delineated in ICD-9. However, we cannot be sure that all individuals given a 'borderline psychosis' diagnosis in 1985 meet criteria for Asperger syndrome. See Isager et al.

(1999) and Mouridsen et al. (1993) for further details of initial selection criteria etc. and how the ICD-9 concepts of 'childhood psychosis' and 'borderline condition' relate to contemporary ICD-10 diagnostic categories, which are used in the current study.

Altogether 341 patients fulfilled the inclusion criteria of the study. Characteristics of the 118 patients with childhood autism, 89 with atypical autism, 13 with other childhood disintegrative disorder and 121 with Asperger syndrome at assessment in childhood are shown in Table1.

Methods

All patients entered into the study on the date of their first admission for ASD. Information about whether the patient was deceased, had emigrated, or had disappeared was obtained by record linkage to the Danish Central Persons Registry using the citizen's personal identification number, which ensures a definitive identification, and made it possible to follow up all

Table 1 **Selected characteristics of 341 persons with autism spectrum disorders at assessment in childhood and at follow-up, 18 April 2006**

	Childhood autism	*Atypical autism*	*Other childhood disintegrative disorders*	*Asperger syndrome*
Number	118	89	13	121
Admission age:				
Mean (SD)	5.4 (2.5)	9.0 (4.0)	5.9 (1.5)	9.7 (3.1)
Range	2–15	3–17	3–8	3–17
Gender:				
Male	85	58	9	104
Female	33	31	4	17
Intelligence:				
<50	53	20	7	0
50–69	30	15	2	16
>69	34	53	4	105
Unknown	1	1	0	0
Age at follow-up:				
Mean	41.5	44.9	40.6	44.3
Range	26–56	27–61	27–52	28–60
Deceased*:				
No. (%)	7 (5.9)	7 (7.9)	2 (15.4)	10 (8.3)
Male, female	4, 3	4, 3	2, 0	8, 2

* The groups do not differ significantly with respect to crude mortality rates.

patients until the end of the study on 18 April 2006. If the patient had deceased, the date of death was recorded and the causes were established by record linkage to the nationwide Cause of Death Registry, which has data about all deaths since 1943 (Juel and Helweg-Larsen, 1999).

Data on deaths in the Danish population, distributed by gender, age and calendar year, were derived from the same official registers. The expected number of deaths in the cohort based on general population mortality rates was estimated for each sex by multiplying the age- and period-specific person-years of observation by the similar age- and period-specific population death rate. Standardized mortality ratios (SMRs) and excess death rates (EDRs) were estimated and 95 percent confidence intervals (CI) were established assuming that the numbers of deaths followed a Poisson distribution. The SMR is the quotient of the observed to the expected numbers of deaths, and value greater than one indicates that the observed mortality exceeds expectations. SMR is frequently used to measure excessive mortality. However, EDR defined as the observed minus expected number of deaths per 1000 person-years is preferred when comparing groups with different baseline mortality. For instance, if excessive mortality is compared between sexes or different age groups, EDR should be chosen. Survival curves for persons with ASD and the matched general population were calculated by actuarial methods.

Results

On the date of our census, 312 of 341 patients were registered as alive and living in Denmark; two were known to have emigrated, and one was registered as 'disappeared' since 1986. The mean age for the patients surveyed was 43.4 (range 26.2–60.5) years and mean follow-up time was 35.5 (range 21.3–47.0) years. Twenty-six patients (7.6%; 18 male and eight female) had died during the 1960–2006 period. Details of crude mortality rates in the ASD subgroups are shown in Table 1. The four groups do not differ significantly with respect to crude mortality rates.

The expected number of deaths was 13.5 (11.5 for males and 2.0 for females), so the SMR was 1.93 (CI 1.26–2.82) for the whole group (Table 2). Thus we found an almost twofold higher mortality rate in ASD compared to the sex- and age-matched Danish population. The excess mortality risk was higher for females (SMR = 4.01; CI 1.73–7.90) than for males (SMR = 1.57; CI 0.93–2.48). Also excess death rate was higher for women (EDR = 2.1; CI 0.5–4.7) than for men (EDR = 0.7; CI −0.1–1.9). The excess mortality rate was more stable for males (SMR varying between 1.42 and 1.98) than for females (SMR varying between 3.17 and 5.22) during the 45 years of follow-up. The increased risk was particularly high during the

Table 2 **Study population, person-years at risk, and observed and expected number of deaths**

Sex	*Number of persons under observation*	*Person-years at risk*	*Observed number of deaths*	*Expected number of deaths*
Men	256	8744.8	18	11.5
Women	85	2921.7	8	2.0
All	341	11,666.5	26	13.5

first 15 years after diagnosis (SMR = 2.40) (Table 3). The excess mortality of ASD compared with the general Danish population is illustrated in Figure 1, which shows survival curves for ASD patients and the general population.

Stratification of cases into two categories, IQ <70 (severe and moderate mental retardation) and IQ >70, showed no significant difference between the two categories with respect to mortality risk (12/143 versus14/196; $p = 0.7$; Fisher's exact test).

Death certificates were obtained for all deceased participants. Selected characteristics and circumstances of death for individuals in each of the

Table 3 **Standardized mortality ratios (SMRs)[a] and excess death rates (EDRs)[b] by sex and years after diagnosis in persons with autism spectrum disorders in Denmark: end of follow-up, 18 April 2006**

Years after diagnosis	*SMR (95% confidence interval)*		
	Men	*Women*	*All*
0–15	1.98 (0.64–4.61)	5.22 (0.63–18.9)	2.40 (0.97–4.95)
15–30	1.42 (0.52–3.10)	3.17 (0.38–11.4)	1.65 (0.71–3.25)
30–45	1.47 (0.59–3.04)	4.08 (1.11–10.4)	1.92 (0.96–3.43)
0–45	1.57 (0.93–2.48)	4.01 (1.73–7.90)	1.93 (1.26–2.82)
Years after diagnosis	*EDR (95% confidence interval)*		
	Men	*Women*	*All*
0–15	0.6 (–0.2–2.4)	1.3 (–0.1–5.4)	0.8 (–0.0–2.3)
15–30	0.5 (–0.6–2.6)	1.2 (–0.3–5.8)	0.7 (–0.3–2.4)
30–45	1.4 (–1.2–6.1)	5.8 (0.2–17.7)	2.5 (–0.1–6.6)
0–45	0.7 (–0.1–1.9)	2.1 (0.5–4.7)	1.1 (0.3–2.1)

[a] Quotient of observed to expected numbers of deaths.
[b] Observed minus expected number of deaths per 1000 person-years.

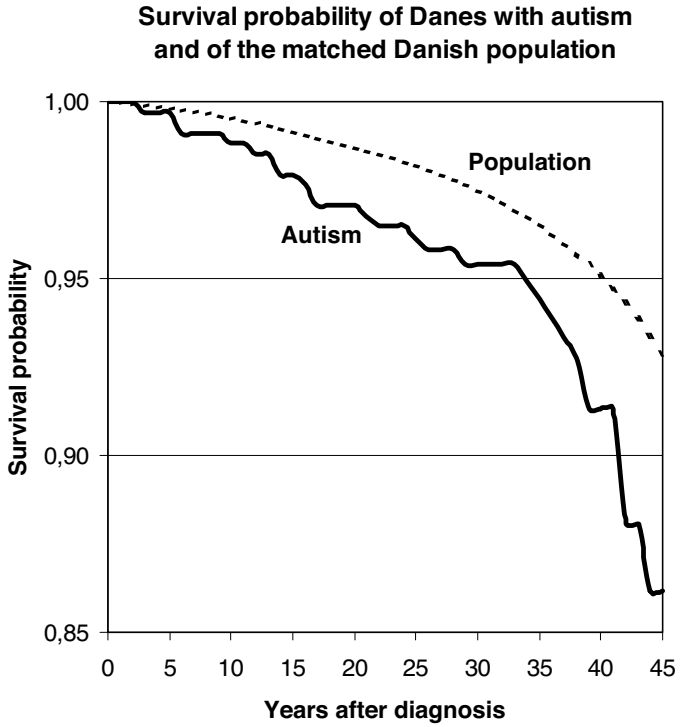

Figure 1 **Survival probability of Danes with autism and of the matched Danish population**

diagnostic subgroups are described in Table 4. Five individuals were recorded as having died from unnatural causes, three in accidents (suffocation and drowning), and two by suicide. Among the 14 persons who had died since our first follow-up in 1993, no one had died due to unnatural causes. On the other hand, diseases of the circulatory system, which were not described in the first observation period, were associated with death in five individuals in the 1993–2006 period.

Among the 26 deaths in people with ASD, epilepsy was present in eight cases, and epilepsy was indicated on four death certificates (one male and three females) as the underlying or contributing cause of death (SMR = 35.0; CI 9.5–89.6). Epilepsy was notably marked in deceased females; five of the eight female deceased had epilepsy.

Different kinds of infectious diseases (meningitis, pneumonia, appendicitis) were associated with death in seven individuals.

Table 4 **Psychiatric and somatic diagnoses, living arrangements and causes of death* (modified from Isager et al. (1999)**

Case	*Admission*					*Conditions of death*			
	Age (years)	*Sex*	*Diagnosis*	*IQ*	*Physical disease*	*Age (years)*	*Residence*	*Natural causes*	*Unnatural causes*
1	4	M	CA	SMR	Hydrocephalus, epilepsy	15	Institution		Accident (suffocation)
2	4	F	CA	SMR	Epilepsy	30	Institution		Accident (suffocation)
3	15	F	CA	SMR	Epilepsy	24	Institution	Meningitis	
4	8[a]	M	CA	SMR		45	Institution	Malignant non-Hodgkin's lymphoma	
5	7[a]	F	CA	SMR	Primary adrenal insufficiency	45	Institution	Cardiomyopathy	
6	4[a]	M	CA	MMR	Emaciation	47	Institution	Pneumonia	
7	4	M	CA	A	Hodgkin's disease	20	Institution	Pneumonia	
8	6	M	DD	SMR	Tuberous sclerosis, renal tumour	31	Institution	Uretheal bleeding	
9	6	M	DD	A	Subacute sclerosing panencephalitis	9	Institution	Pneumonia	
10	5	F	AA	SMR	Epilepsy	18	With parents	Epileptic attack?	
11	5[a]	F	AA	SMR	Epilepsy, chromosomal anomaly	38	Institution	Epileptic attack	
12	12[a]	M	AA	MMR		53	Own apartment	Malignant pulmonary neoplasm	
13	14	M	AA	A		20	With parents		Accident? (overdose)

Continued over

Table 4 **Continued**

Case	*Admission*					*Conditions of death*			
	Age (years)	*Sex*	*Diagnosis*	*IQ*	*Physical disease*	*Age (years)*	*Residence*	*Natural causes*	*Unnatural causes*
14	12	M	AA	A		18	Own apartment		Suicide (overdose)
15	9[a]	M	AA	A	Cardiac atherosclerosis	51	Institution	Acute myocardial infarction	
16	9[a]	F	AA	A	Cardiomyopathy	48	Institution	Cardiac incompensation	
17	7	M	AS	MMR	Epilepsy	36	Unknown	Epileptic attack	
18	6[a]	M	AS	MMR	Becker muscular dystrophy	42	Institution	Pneumonia	
19	5	M	AS	A		25	Institution		Suicide (jump)
20	6	M	AS	A	Epilepsy	19	With parents		Accident (drowning)
21	10[a]	M	AS	A		45	Own apartment	Acute ischaemic heart disease	
22	13[a]	M	AS	A		30	Own apartment	Unknown, found dead	
23	15[a]	M	AS	A	Diverticle of Meckel septicaemia	30	Institution	Acute appendicitis	
24	13[a]	M	AS	A		47	Institution	Acute myocardial infarction	
25	5[a]	F	AS	A	Polycystic syndrome	47	Institution	Septicaemia, cardiac incompensation	
26	11[a]	F	AS	A	Epilepsy	32	Institution	Epileptic attack?	

CA indicates childhood autism; AA atypical autism; DD other disintegrative disorder; AS Asperger syndrome.
SMR indicates severe mental retardation (IQ <50); MMR mild mental retardation (IQ 50–70), A average intelligence (IQ >70).
[a] Died in the 1993–2006 period.

Discussion

The aim of the current study was to update our previous study (Isager et al., 1999) of mortality and causes of death in a nationwide sample of 341 Danish individuals with ASD, now on average 43 (range 26–60) years of age.

Systematic studies dealing with mortality and causes of death in ASD are rare. There are difficulties in creating a sufficient sample size, in tracing all participants for a sufficient time span, and in establishing the cause(s) of death. In the current study, the limited number of ASD cases made it impossible to compare cause-specific death rates with numbers expected according to the general population mortality, with the exception of epilepsy. Cause-specific mortality offers baseline information for health promotion and preventive work.

As observed earlier (Isager et al., 1999), and in agreement with the findings of Shavelle and colleagues (Pickett et al., 2006; Shavelle et al., 2001), the mortality among those with ASD was nearly twice that of the general population (SMR = 1.93). Similar to the Shavelle et al. (2001) study, the SMR in our group of patients was particularly high in females (SMR = 4.01). The (statistically non-significant) higher SMR for women than men partly reflects the fact that the general mortality risk is higher for men than women. However, the EDR was also slightly higher for women than men, but the difference between sexes was not statistically significant. Further research is needed on the male/female differences.

The distribution of unnatural causes of death and diseases of the circulatory system in the two study periods suggests that the events surrounding the death of young people differ from those for older people with ASD.

Deaths associated with epilepsy and infectious diseases were common in the current study. Epilepsy has been associated with death in a number of studies (Bailey et al., 1998; Billstedt et al., 2005; Howlin et al., 2004; Shavelle et al., 2001). In the current study, eight of the 26 who died had epilepsy. Mortality in epilepsy is known to be about two to three times higher than in the general population, the ratio being higher at younger ages (Annegers and Coan, 1999). Our results indicate an even higher excess mortality from epilepsy and underscore that, in preventive work, special attention should focus on this group of autistic people.

Prevention efforts to decrease mortality in individuals with ASD may need to address the conditions that are the immediate causes of deaths (i.e. infectious diseases and epilepsy). The current findings underscore the importance of maintaining sufficient competence levels in the fields of internal medicine and neurology within the ASD care system to recognize and properly treat somatic as well as psychiatric illness. It is necessary to maintain this competence in order to develop optimal cooperation with these disciplines.

Deficits in communication, in some cases amounting to lack of functional speech, and social understanding are two of the three domains that define ASD. In addition, some ASD individuals are insensitive to cold and pain (Bailey et al., 1998) and severe mental retardation is present in many CA cases (Table 1). These deficits often make medical care difficult and can lead to an exacerbation in the state of somatic illness or diagnostic delay, eventually leading to death-causing illness (Larsen and Mouridsen, 1997). In the current study, patient 3 illustrates this risk. Moreover, as many ASD individuals are dependent on stability and dislike changes in daily routines, implementation of or change of medical care can be difficult to accomplish. In many cases a differential diagnosis cannot be made on the basis of an ordinary clinical interview, and detailed information will be needed from staff in order to distinguish between behaviours caused by ASD and those caused by the additional somatic disorder.

In the current study, three patients died due to accidents (suffocation and drowning). Patients 1 and 2 lived in specialized institutions for autistic people. In both cases, the patients managed to swallow dangerous objects and choke on them during an unsupervised period. Different kinds of accidents have been reported in other studies too. In the Fombonne et al. (1989) study, three had died from road accidents. One of the three deaths in the study of Ballaban-Gil et al. (1996) followed drowning. Two of the six deaths in the autopsy study of Bauman and Kemper (1994) were also caused by drowning. Suffocation and drowning was also relatively common in the study of Shavelle et al. (2001). These findings illustrate that poor social communication may well predispose autistic individuals to accidental death (Ballaban-Gil et al., 1996). Since accidents are avoidable in some cases, special attention should be paid to community surroundings.

In summary, avoidable deaths might be reduced by making direct care staff more aware of the risks and better trained in acute care, along with monitoring of special incidents. If we intend to decrease the avoidable mortality in ASD, then we need to focus especially on risks of accidents and on preventing infectious diseases. Future staff education should focus on a better management of the complex relationship between ASD and physical illness. It would also be appropriate for states or local authorities to assess staff competence on a regular basis.

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