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In-hospital mortality among adults with autism spectrum disorder in the United States: A retrospective analysis of US hospital discharge data

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Abstract

A retrospective data analysis using 2004–2014 Healthcare Cost and Utilization Project Nationwide Inpatient Sample was conducted to examine in-hospital mortality among adults with autism spectrum disorders in the United States compared to individuals in the general population. We modeled logistic regressions to compare inpatient hospital mortality between adults with autism spectrum disorders (n = 34,237) and age-matched and sex-matched controls (n = 102,711) in a 1:3 ratio. Adults with autism spectrum disorders had higher odds for inpatient hospital mortality than controls (odds ratio = 1.44, 95% confidence interval: 1.29–1.61, $p < 0.001$). This risk remained high even after adjustment for age, sex, race/ethnicity, income, number of comorbidities, epilepsy and psychiatric comorbidities, hospital bed size, hospital region, and hospitalization year (odds ratio = 1.51, 95% confidence interval: 1.33–1.72, $p < 0.001$). Adults with autism spectrum disorders who experienced in-hospital mortality had a higher risk for having 10 out of 27 observed Elixhauser-based medical comorbidities at the time of death, including psychoses, other neurological disorders, diabetes, hypothyroidism, rheumatoid arthritis collagen vascular disease, obesity, weight loss, fluid and electrolyte disorders, deficiency anemias, and paralysis. The results from the interaction of sex and autism spectrum disorders status suggest that women with autism spectrum disorders have almost two times higher odds for in-hospital mortality (odds ratio = 1.95, $p < 0.001$) than men with autism spectrum disorders. The results from the stratified analysis also showed that women with autism spectrum disorders had 3.17 times higher odds (95% confidence interval: 2.50–4.01, $p < 0.001$) of in-hospital mortality compared to women from the non–autism spectrum disorders matched control group; this difference persisted even after adjusting for socioeconomic, clinical, and hospital characteristics (odds ratio = 2.75, 95% confidence interval: 2.09–3.64, $p < 0.001$). Our findings underscore the need for more research to develop better strategies for healthcare and service delivery to people with autism spectrum disorders.

Keywords

adults, autism spectrum disorders, epilepsy, in-hospital mortality, psychiatric comorbidity

Introduction

It is well-documented that people with autism spectrum disorder (ASD) experience a variety of long-term adverse social and health outcomes. These include lower incomes and educational achievement (Roux et al., 2013; Shattuck et al., 2012), poorer physical and mental health (Kalb, Stuart, Freedman, Zablotsky, & Vasa, 2012; Mandell, Thompson, Weintraub, Destefano, & Blank, 2005; Nicolaidis et al., 2012), and reduced quality of life (van Heijst & Geurts, 2015). Prior studies have described the psychiatric and medical conditions that frequently co-occur with, result from, and are associated with ASD (Rubenstein & Bishop-Fitzpatrick, 2019). For example, with respect to mental health conditions, studies have reported considerably higher incidence of psychiatric

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morbidities like anxiety, depression, schizophrenia, and psychosis among people with ASD compared to other individuals (Cochran, Dvir, & Frazier, 2013; Tsakanikos, Sturmey, Costello, Holt, & Bouras, 2007). People with ASD also experience a wide range of physical health comorbidities, including gastrointestinal diseases (Mannion & Leader, 2013), infections (Vohra, Madhavan, & Sambamoorthi, 2017), auditory disorders (Doshi-Velez, Ge, & Kohane, 2014), immunologic conditions (Davignon, Qian, Massolo, & Croen, 2018), among others. A considerable number of studies have also emphasized the frequent co-occurrence of ASD and epilepsy and other seizure disorders (Bolton et al., 2011; Tuchman, Cuccaro, & Alessandri, 2010).

Discouragingly, studies have also shown that the risk of premature mortality among people with ASD is twice that of the general population (Hirvikoski et al., 2016; Mouridsen, Bronnum-Hansen, Rich, & Isager, 2008; Schendel et al., 2016). Furthermore, a population-based study from Sweden (Hirvikoski et al., 2016) found that people with ASD without intellectual disabilities and those with intellectual disabilities died an average of 16 and 30 years earlier than individuals in the general population, respectively. In the United States, Guan and Li (2017b) estimated that individuals with an autism diagnosis died, on average, 36 years younger than individuals in the general population. Little is known about the common causes of mortality in people with ASD and whether and how such causes differ from those in people without ASD. The few epidemiological studies that have considered these questions have found that people with ASD are at a significantly higher risk of dying from unintentional injuries (Guan & Li, 2017b) such as drowning (Guan & Li, 2017a).

To date, neither the Centers for Disease Control and Prevention (CDC) nor other public health care services in the United States have reported on mortality and medical comorbidities in adults with ASD. A comprehensive perspective of the health trajectories of people with ASD is needed to inform program development and strategies that improve their long-term quality of life. In particular, an assessment of the mortality risks and medical comorbidities can inform targeted health interventions, as well as measures to safeguard people with ASD against preventable fatalities. Previous population-based studies on mortality among people with ASD, however, have mostly been conducted in Europe (Sweden and Denmark) (Gillberg, Billstedt, Sundh, & Gillberg, 2010; Hirvikoski et al., 2016; Mouridsen et al., 2008). Although these studies have contributed to researchers' understanding of the health risks to which people with ASD are exposed, the findings may not be generalizable to the United States, which has unique health care and long-term services systems (Nadash, Doty, Mahoney, & Von Schwanenflugel, 2011). The few US-based studies on mortality among people with ASD were limited by relatively small samples and were only representative at the state level (California and Utah) (Bilder et al., 2013; Pickett, Xiu, Tuchman, Dawson, & Lajonchere, 2011; Shavelle & Strauss, 1998; Shavelle, Strauss, & Pickett, 2001). Hence, there is an urgent need for empirical research on a nationally representative sample of US adults with ASD so that appropriate strategies and policies for health care and social services can be implemented.

The Healthcare and Cost Utilization Project National Inpatient Sample (HCUP-NIS; Agency for Healthcare Research and Quality (AHRQ), 2017) was drawn to be representative of all hospital admissions in the United States. Previous research (Andrews, Russo, & Pancholi, 2006; Doshi, Desai, Shah, Decter, & Doshi, 2018; Foxman, Klemstine, & Brown, 2003; Zilberberg et al., 2014) used the HCUP-NIS to describe and evaluate disease-related in-hospital mortality in different population groups. In this study, we attempted to fill the gap in the literature by analyzing the 2004–2014 HCUP-NIS hospital discharge data to describe rates of in-hospital mortality between adults (18 years and older) with and without ASD. We also evaluate the risk for in-hospital mortality in adults with ASD and examined the medical comorbidities of those who experience in-hospital mortality. In addition, given that past studies (Gillberg et al., 2010; Hirvikoski et al., 2016; Mouridsen et al., 2008) have found that women with ASD and those with co-existing epilepsy and psychiatric comorbidities, regardless of sex, were at higher risk of all-cause and cause-specific premature mortality, we examined the potential role of sex, epilepsy, and psychiatric comorbidities as possible moderators of in-hospital mortality. We hypothesized that adults with ASD will have a higher risk of in-hospital mortality and that those who experience in-hospital mortality will also have higher risk for medical comorbidities at the time of death. We also hypothesized that the in-hospital mortality will be moderated by sex, epilepsy, and psychiatric comorbidities.

Methods

Data

We conducted a retrospective matched case-control study using the 2004–2014 HCUP-NIS, the largest all-payer hospital discharge records database. The HCUP-NIS contains hospital discharge data on approximately 8 million hospital stays each year from about 1000 hospitals sampled to approximate a 20% stratified sample of US community hospitals. The sample of hospitals was drawn from between 37 and 47 states (depending on the survey year) and is divided into 60 strata based on geographic region, ownership, location, teaching status, and size. The HCUP-NIS data do not include unique patient identifiers; thus, the unit of analysis is the hospital discharge. Given the nature of these data, it is not possible to ascertain whether there

are duplicate cases; hence, patients may be represented more than once in the data. The HCUP-NIS systematic sample is a self-weighted sample design similar to simple random sampling and is representative of the population on the following hospital and patient factors: hospital, census division of hospital, hospital ownership, urban–rural location of hospital, hospital teaching status, number of beds in the hospital, diagnosis-related group (DRG) for the hospital stay, and admission month of the hospital stay (Houchens et al., 2015). More information about the design of the survey and using the discharge weights for generating national estimates is provided elsewhere (Houchens et al., 2015).

Study population

From the discharge data, records with a primary or secondary diagnosis (*DXn*)[1] of ASD using *International Classification of Diseases, Ninth Edition, Clinical Modifications* (ICD-9-CM) (World Health Organization, 1977) codes 299.0x, 299.8x, or 299.9x were extracted. Only records of people aged (*AGE*) 18 years and older were included, yielding a sample of case records of adults with ASD. This method of ASD case ascertainment has been widely used (Bush, Connelly, Perez, Barlow, & Chiang, 2017; Croen et al., 2015; Leslie & Martin, 2007). Of note, because of the structure of the HCUP-NIS data and that it includes discharge records and not records or claims linkable with a patient identifier, we were unable to use the preferable approach (Mandell, Cao, Ittenbach, & Pinto-Martin, 2006; Wang, Mandell, Lawer, Cidav, & Leslie, 2013) of identifying ASD based on two or more outpatient claims on two different days or at least one inpatient claim or discharge record with an ASD diagnosis. A total of 34,237 discharge records for adults with ASD were identified for the 2004–2014 study period. The control group with no record of ASD (n = 102,801), similar to previous research (Lokhandwala, Khanna, & West-Strum, 2012), was age matched and sex matched in 1:3 case-control ratio using the greedy matching algorithm (Austin, 2011).

In addition, we identified specific subgroups of adults with ASD who also have co-occurring epilepsy and psychiatric comorbidities. Adults with epilepsy were identified based on whether their discharge record did or did not have a primary or secondary diagnosis (*DXn*) of epilepsy (ICD-9-CM code 345.xx). Patients with co-existing psychiatric comorbidities were identified based on the codes used by Croen et al. (2015), which included alcohol abuse, alcohol dependence, anxiety disorder, bipolar disorder, attention-deficit disorders, dementia, depression, drug abuse, drug dependence, obsessive–compulsive disorder, other psychoses, schizophrenic disorders, and suicide attempts (see Appendix 1 for ICD-9-CM codes used to identify each condition).

Measures

In-hospital mortality

In-hospital mortality was measured as a dichotomous variable (yes/no) based on the information from hospital discharge records for patients who died (*DIED*) during hospitalization (1.35%, 462 adults with ASD, 1.02%, 1047 control group members).

Medical comorbidities

We categorized the medical comorbidities using the 29 Elixhauser comorbidities identified by AHRQ using standard methods by Elixhauser, Steiner, Harris, and Coffey (1998) and measured as a dichotomous variable (yes/no). Elixhauser comorbidities are clinical conditions that exist prior to a patient's admission to the hospital and are not related to the principal reason for hospital admission, but considered to be a significant factor influencing in-hospital mortality (Elixhauser et al., 1998). More information about how the Elixhauser comorbidity method assigns variables that identify comorbidities in hospital discharge records using the ICD-9-CM and the DRG can be found elsewhere (Healthcare Cost and Utilization Project (HCUP), 2019).

Demographic and socioeconomic characteristics

Demographic and socioeconomic characteristics included age (*AGE*; 18–20; 21–45; or 46+ years), sex (*FEMALE*), race/ethnicity (*RACE*; non-Hispanic White, non-Hispanic Black, Hispanic, Other race/ethnicity, and non-identified race/ethnicity), the primary insurance (*PAY1*; Medicare, Medicaid, private, or uninsured), and median household income for the individual's five-digit zip code (*ZIPINC_QRTL*; <US$38,999; US$39,000–US$47,999; US$48,000–US$62,999; or US$63,000+).

Clinical characteristics

Clinical characteristics included the number of comorbidities and was based on AHRQ Elixhauser Comorbidities (Elixhauser et al., 1998) and measured as a categorical variable (none, 1, 2, 3, or 4+).

Hospital characteristics

Hospital characteristics included hospital bed size (*HOSP_BEDSIZE*; small, medium, or large), based on the total number of hospital beds and adjusted for the hospital's location and teaching status (AHRQ, 2008), and the region of the hospital (*HOSP_REGION*; Northeast, Midwest, South, or West).

Statistical analysis

Demographic, socioeconomic, clinical, and hospital characteristics were compared for adults with ASD and the matched control group. Differences across categorical variables and continuous variables between the two clinical populations were evaluated using chi-square tests and t-tests, respectively. Hospital discharge weights were applied to the sample data for all bivariate statistics to create national estimates. The risk for in-hospital mortality in adults with ASD and matched control group (referent) were compared using logistic regressions. Logistic regression was also used to assess the risk for different medical comorbidities in adults with ASD who experienced in-hospital mortality compared to a matched control group (referent). The logistic regression coefficients and the 95% confidence interval (CI) were estimated as unadjusted and adjusted odds ratios (ORs). Recall that our unadjusted models already adjust for age and sex because the case-control matching was based on age and sex. Multivariable models adjusted for demographic and socioeconomic characteristics (age, sex, race/ethnicity, type of health insurance, median household income for patients' zip code), clinical characteristics (number of Elixhauser comorbidities, epilepsy, and psychiatric comorbidities), and hospital characteristics (hospital bed size and region of the hospital). Furthermore, we tested for the moderating effect of sex and diagnosis of epilepsy and psychiatric comorbidities by including interaction terms between these variables and ASD in the regression models. The results from the interaction analysis were reported in OR metric (UCLA: Statistical Consulting Group, 2019) by multiplying the coefficients for the OR of the interaction terms (e.g. ASD × sex) and the coefficients for the OR of the main effects (e.g. sex). Finally, we conducted stratified analysis by sex, diagnosis of epilepsy, and the presence of psychiatric comorbidities, by comparing the ORs and 95% CI derived from each ASD group versus control (e.g. adults with ASD and epilepsy vs controls with epilepsy). All models were estimated with robust standard errors clustered on the hospital identifier using Stata, version 15 MP (StataCorp, 2015), and a p value of <0.05 was the accepted level of significance. In addition, because a number of model covariates had missing values (insurance (*PAY1*): 0.3%, income (INC_QRTL): 3.1%, hospital bed size (*HOSP_BEDSIZE*): 0.6%), consistent with best practices (Royston, 2011; Schenker et al., 2006), we conducted multiple imputations by chained equations to impute values for the variables with missing data.

The study was approved by the authors' Institutional Review Board.

Results

A description of the sample and weighted statistics comparing ASD adults with sex- and age-matched control group are presented in Table 1. Compared to the matched control group, those with ASD were more likely to be non-Hispanic White, have public primary health insurance such as Medicare or Medicaid, and were more likely to be from non-poor neighborhoods. Adults with ASD were more likely to have psychiatric comorbidities and more than six times as likely to have epilepsy than adults in the matched control group.

In-hospital mortality

A total of 462 (1.35%) adults with ASD died during hospitalizations in the United States over the study period compared with 967 (0.95%) of the matched controls (Table 2). Adults with ASD had 1.44 times higher odds (95% CI: 1.29–1.61, $p<0.001$) of in-hospital mortality, compared with matched control group (Table 2). The odds of in-hospital mortality among adults with ASD increased after further adjustment for demographic, socioeconomic, clinical, and hospital characteristics (OR = 1.51, 95% CI: 1.33–172, $p<0.001$). In general, women had significantly lower risk for in-hospital mortality (OR = 0.74, 95% CI: 0.65–0.85, $p<0.001$) compared to men. Adults who had epilepsy compared to adults without had significantly higher risk of in-hospital mortality (OR = 1.57, 95% CI: 1.33–1.84, $p<0.001$). However, after adjustment was made, this risk was fully explained by differences in socioeconomic, clinical, and hospital characteristics (OR = 0.91, 95% CI: 0.76–1.08, $p<0.001$). Adults with psychiatric comorbidities compared to adults without psychiatric comorbidities had more than two times lower odds of in-hospital mortality (OR = 0.45, 95% CI: 0.40–0.51, $p<0.001$). After further adjustment, the odds become even lower (OR = 0.32, 95% CI: 0.28–0.36, $p<0.001$).

Moderation of in-hospital mortality

The results from the interaction of sex and ASD suggest that women with ASD have almost two times higher odds for in-hospital mortality (OR = 1.95, $p<0.001$) than men with ASD (Table 2). We also found evidence of moderation of the risk of in-hospital mortality among adults with ASD by psychiatric comorbidities. Namely, adults with ASD who have psychiatric comorbidities had almost four times lower odds (OR = 0.23, $p<0.001$) of in-hospital mortality than adults with ASD who do not have psychiatric comorbidities. We found no evidence of moderation of the risk of in-hospital mortality among adults with ASD with or without epilepsy.

The results from the stratified analysis also showed that women with ASD had 3.17 times higher odds (95% CI: 2.50–4.01, $p<0.001$) of in-hospital mortality compared to women from the non-ASD matched control group; this difference persisted even after adjusting for socioeconomic, clinical, and hospital characteristics (OR = 2.75, 95% CI: 2.09–3.64, $p<0.001$; Table 3). Men with ASD, after

Table 1. Sample characteristics in the adults with ASD and matched control groups, United States, 2004–2014, N = 136,948.

Characteristic	ASD		Control		p value[a]
	Freq.	%	Freq.	%	
N (unweighted)	34,237	100	102,711	100	
N (weighted)	166,360	100	497,486	100	
Sex					0.997
Male	25,772	75.3	77,319	75.3	
Female	8465	24.7	25,392	24.7	
Race and ethnic identity					<0.001
Non-Hispanic White	22,139	64.7	52,853	51.5	
Non-Hispanic Black	3691	10.8	17,092	16.6	
Hispanic	1843	5.4	13,067	12.8	
Non-Hispanic Other	1505	4.4	6278	6.1	
Unknown Race/Ethnicity	5059	14.7	13,421	13.0	
Age (years)					0.976
18–34	21,986	64.3	65,950	64.3	
35–54	8258	24.0	24,783	24.1	
55+	3993	11.7	11,978	11.7	
Mean (SD)	33.1	0.08	33.1	0.04	<0.001
Primary insurance					
Medicare	12,355	36.0	12,998	12.7	
Medicaid	11,309	33.2	27,190	26.6	
Private insurance	8757	25.6	40,383	39.4	
Uninsured	1764	5.2	21,836	21.2	
Median household income for patient's zip code					<0.001
US$1–US$38,999	7788	23.5	31,635	31.8	
US$39,000–US$47,999	8327	25.1	25,695	25.8	
US$48,000–US$62,999	8478	25.6	22,949	23.0	
US$63,000+	8557	25.8	19,287	19.4	
Have epilepsy					
No	26,926	78.6	99,162	96.5	<0.001
Yes	7311	21.4	3549	3.5	
Has psychiatric comorbidities					
No	15,831	46.1	66,800	64.9	<0.001
Yes	18,406	53.9	35,911	35.1	
Number of Elixhauser comorbidities[b]					
None	8774	25.6	38,087	37.0	<0.001
1	9911	28.9	26,015	25.4	
2	7398	21.6	17,856	17.4	
3	4317	12.6	10,350	10.1	
4+	3837	11.2	10,403	10.2	
Hospital bed size					0.031
Small (1–49 beds)	4304	12.2	12,700	12.1	
Medium (50–99 beds)	7987	23.6	25,295	25.0	
Large (⩾100 beds)	21,749	64.1	64,030	62.9	
Region of hospital					<0.001
Northeast	9236	27.2	20,627	20.3	
Midwest	9655	28.3	23,195	22.7	
South	9480	27.5	38,759	37.4	
West	5866	17.1	20,130	19.6	

Source: Healthcare Cost and Utilization Project, National Inpatient Sample (HCUP-NIS) data, 2004–2014.

ASD: autism spectrum disorder; SD: standard deviation.

[a]The p values are based on chi-squared test for categorical variables and t-test for continuous variables.

[b]Number of Elixhauser comorbidities was based on the Agency for Health Care Research and Quality (AHRQ) standard methods by Elixhauser, Steiner, Harris, and Coffey (1998).

Table 2. Risk for in-hospital mortality for adults with ASD and matched control groups, United States, 2004–2014, N = 136,948.

Sample characteristic	Deaths, N (%)	Unadjusted[a]		Adjusted[b]	
		OR	95% CI	OR	95% CI
Study groups					
Control	967(0.95)	Reference		Reference	
ASD	462 (1.35)	1.44***	(1.29–1.61)	1.51***	(1.33–1.72)
Sex					
Male	1149 (1.11)	Reference		Reference	
Female	280 (0.83)	0.74***	(0.65–0.84)	0.74***	(0.65–0.85)
Have epilepsy					
No	1260 (1.00)	Reference		Reference	
Yes	169 (1.56)	1.57***	(1.33–1.84)	0.91	(0.76–1.08)
Has psychiatric comorbidities					
No	1099 (1.33)	Reference		Reference	
Yes	330 (0.61)	0.45***	(0.40–0.51)	0.32***	(0.28–0.36)
Interaction terms[c]					
ASD × sex				2.63***	(2.00–3.45)
Male with ASD	–	–	–	Reference	
Female with ASD	–	–	–	1.95***	–
ASD × epilepsy				0.84	(0.58–1.21)
ASD person without epilepsy	–	–	–	Reference	
ASD person with epilepsy	–	–	–	0.76	–
ASD × psychiatric comorbidities				0.72**	(0.55–0.95)
ASD person without psychiatric comorbidities	–	–	–	Reference	
ASD person with psychiatric comorbidities	–	–	–	0.23**	–

Source: Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) data, 2004–2014.ASD: autism spectrum disorder; OR: odds ratios; CI: confidence intervals.

[a]Unadjusted models are already adjusted for differences in age and sex after case-control matching was done based on age and sex.

[b]Adjusted for age, race/ethnicity, type of health insurance, median household income for patients' zip code, number of Elixhauser medical comorbidities, hospital bed size, and region of the hospital.

[c]The results from interaction analysis are reported in odds ratio metric (UCLA: Statistical Consulting Group, 2019) by multiplying the coefficients for the odds ratio of the interaction terms (e.g. ASD × sex) and the coefficients for the odds ratio of the main effects (e.g. sex).

*** $p < 0.01$, ** $p < 0.05$, and * $p < 0.1$.

Table 3. Risk for in-hospital mortality for adults with ASD and matched control groups stratified by sex, diagnosis of epilepsy, and psychiatric comorbidities, United States, 2004–2014.

Characteristic of ASD Adult	ASD		Control					
	Deaths		Deaths		Unadjusted model[a]		Adjusted model[b]	
	N	%	N	%	OR	95% CI	OR	95% CI
Female, n = 33,857	143	1.69	137	0.54	3.17***	(2.50–4.01)	2.75***	(2.09–3.64)
Male, n = 103,091	319	1.24	830	1.07	1.15**	(1.01–1.32)	1.25***	(1.08–1.45)
Have epilepsy, n = 10,860	121	1.66	48	1.35	1.23	(0.88–1.72)	1.33	(0.92–1.94)
Has psychiatric comorbidities, n = 54,317	108	0.59	222	0.62	0.95	(0.75–1.19)	1.18	(0.91–1.52)

Source: Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) data, 2004–2014.ASD: autism spectrum disorder; CI: confidence intervals; OR: odds ratios.

[a]Unadjusted models are already adjusted for differences in age and sex after case-control matching was done based on age and sex.

[b]Adjusted for age, sex, race/ethnicity, type of health insurance, median household income for patients' zip code, number of Elixhauser medical comorbidities, epilepsy, psychiatric comorbidities, hospital bed size, and region of the hospital.

*** $p < 0.01$, ** $p < 0.05$, and * $p < 0.1$.

adjustment, had 1.25 times higher odds (95% CI: 1.08–1.45, $p < 0.001$) of in-hospital mortality compared to men from the matched control group. However, the results from the stratified analysis did not support the protective nature of psychiatric comorbidities from the interaction analysis and we did not find significant differences in in-hospital

Table 4. The odds ratios for medical comorbidities among adults with ASD and matched control groups who experienced in-hospital mortality, United States, 2004–2014 (N = 136,948).

Medical comorbidities	ASD (n = 34,237)		Control (n = 102,711)		OR	95% CI
	Deaths		Deaths			
	N	%	N	%		
All deaths	462	100.0	967	100.0		
Congestive heart failure	39	8.3	115	11.9	1.02	0.71–1.46
Valvular disease	16	3.5	26	2.7	1.85*	0.99–3.44
Pulmonary circulation disease	23	4.9	53	5.5	1.30	0.80–2.12
Peripheral vascular disease	17	3.7	63	6.5	0.81	0.47–1.38
Paralysis	52	11.1	53	5.5	2.95***	2.01–4.32
Other neurological disorders	147	31.8	85	8.8	5.21***	3.98–6.80
Pulmonary circulation disease	39	8.3	147	15.2	0.80	0.56–1.13
Diabetes without chronic complications	53	11.5	114	11.8	1.40**	1.01–1.93
Diabetes with chronic complications	<11	1.3	31	3.2	0.58	0.24–1.39
Hypothyroidism	61	13.2	41	4.2	4.47***	3.01–6.64
Renal failure	39	8.3	123	12.7	0.95	0.66–1.36
Liver disease	17	3.7	84	8.7	0.61*	0.36–1.02
Peptic ulcer disease and bleeding	NA	NA	NA	NA	NA	NA
Acquired immune deficiency syndrome	NA	NA	NA	NA	NA	NA
Lymphoma	<11	0.9	16	1.7	0.75	0.25–2.24
Metastatic cancer	18	3.9	87	9.0	0.62*	0.37–1.03
Solid tumor w/o metastasis	<11	1.9	22	2.3	1.23	0.57–2.67
Rheumatoid arthritis collagen vascular diseases	11	2.4	11	1.1	3.00***	1.30–6.92
Coagulopathy	81	17.3	222	23.0	1.09	0.85–1.41
Obesity	35	7.6	47	4.9	2.24***	1.44–3.46
Weight loss	65	13.9	129	13.3	1.51***	1.12–2.04
Fluid and electrolyte disorders	262	56.7	486	50.3	1.62***	1.40–1.89
Chronic blood loss anemia	<11	0.6	12	1.2	0.75	0.21–2.66
Deficiency anemias	84	18.2	153	15.8	1.65***	1.26–2.15
Alcohol abuse	<11	0.4	99	10.2	0.06***	0.01–0.25
Drug abuse	<11	1.1	76	7.9	0.20***	0.08–0.49
Psychoses	54	11.5	24	2.5	6.76***	4.18–10.93
Depression	18	3.9	50	5.2	1.08	0.63–1.85
Hypertension	90	19.2	277	28.6	0.97	0.77–1.24

Source: Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) data, 2004–2014.
ASD: autism spectrum disorder; CI: confidence intervals; OR: odds ratios; CD-9: International Classification of Diseases, Ninth Edition.We summarized the specific underlying causes of deaths based on the Agency for Healthcare Research and Quality (AHRQ) Elixhauser Comorbidity Index (Elixhauser, Steiner, Harris, & Coffey, 1998). To maintain confidentiality, cells with <11 cases cannot be reported.
*** $p<0.01$, ** $p<0.05$, and * $p<0.1$.

mortality between adults with ASD and psychiatric comorbidities and adults with psychiatric comorbidities from the matched control group. No differences in the in-hospital mortality were observed between adults with ASD and adults from the matched control group by epilepsy.

Medical comorbidities

In addition to the higher in-hospital mortality risk among adults with ASD compared to the matched control group, we also observed different patterns of higher risk for select medical comorbidities among those who experienced in-hospital mortality. Adults with ASD who experienced in-hospital mortality, compared to their counterparts from a matched control group, had a higher risk for having 10 out of 27 observed Elixhauser-based medical comorbidities at the time of death. The ORs were highest for psychoses (OR = 6.76, 95% CI: 4.18–10.93, $p < 0.001$), followed by other neurological disorders (OR = 5.21, 95% CI: 3.98–6.80, $p < 0.001$), hypothyroidism (OR = 4.47, 95% CI: 3.01–6.64, $p < 0.001$), rheumatoid arthritis collagen vascular diseases (OR = 3.00, 95% CI: 1.30–6.92, $p < 0.001$), paralysis (OR = 3.00, 95% CI: 1.30–6.92, $p < 0.001$), obesity (OR = 2.24, 95% CI: 1.44–3.46, $p < 0.001$), deficiency anemias (OR = 1.65, 95% CI: 1.26–2.15, $p < 0.001$), fluid and electrolyte disorders (OR = 1.62, 95% CI: 1.40–1.89,

$p < 0.001$), weight loss (OR = 1.51, 95% CI: 1.12–2.04, $p < 0.001$), and diabetes without chronic complications (OR = 1.40, 95% CI: 1.01–1.93, $p < 0.001$; Table 4). The risk of having a comorbidity related to alcohol and drug abuse was significantly lower among adults with ASD who experienced in-hospital mortality compared to their counterparts from the matched control group (OR = 0.06, 95% CI: 0.01–0.25, $p < 0.001$ and OR = 0.20, 95% CI: 0.08–0.49, $p < 0.001$, respectively).

Medical comorbidities by sex

Compared to their counterparts from the matched control group, both women and men with ASD who experienced in-hospital mortality were at higher risk for select medical comorbidities. Women with ASD who experienced in-hospital mortality, compared to their counterparts from the matched control group, had a higher risk of 10 out of 22 observed Elixhauser-based medical comorbidities. The largest differences in risk between women with and without ASD were for other neurological disorders, followed by psychoses, paralysis, rheumatoid arthritis collagen vascular disease, deficiency anemias, hypothyroidism, weight loss, fluid and electrolyte disorders, obesity, and congestive heart failure (Table 5). Men with ASD who experienced in-hospital mortality, compared to their counterparts in the matched control group, had a higher risk of 6 out of 27 observed Elixhauser-based medical comorbidities. The largest differences in risk for men with and without ASD were for hypothyroidism, followed by psychoses, other neurological disorders, obesity, paralysis, and fluid and electrolyte disorders. Unlike in the women cohort, the risk of in-hospital mortality for alcohol and drug abuse, liver disease, and metastatic cancer were significantly lower among men with ASD compared to the men from matched control group.

Discussion

This study provides the first comprehensive account of the in-hospital mortality among adults with autism in the United States based on analysis of nationally representative hospital discharge records data. The results of this study confirm our hypothesis that adults with ASD are at a higher risk for in-hospital mortality compared to non-ASD adults, although the increased risk of in-hospital mortality was not large enough to be clinically meaningful.

This study builds on earlier studies that have identified an increased risk for premature mortality among adults with ASD compared to non-ASD adults. We extend these studies in several ways. First, among those who experienced in-hospital mortality, we have provided evidence of clinically meaningful differences for select Elixhauser-based medical comorbidities between people with and without ASD.

Second, we conducted a stratified analysis by sex and by diagnoses of psychiatric comorbidities and epilepsy. In the sex-stratified analysis, both female and male adults with ASD were found to be at higher risk of in-hospital mortality compared to their respective peers from the general population. Notably, among people with ASD, women with ASD had also higher risk for in-hospital mortality than their male counterparts with ASD. Interestingly, we found no risk of in-hospital mortality by epilepsy in the general population and within the ASD population. We also found a significantly lower risk for in-hospital mortality in the general population and in the ASD population by psychiatric comorbidities. However, when the risk of in-hospital mortality was compared for the population with psychiatric comorbidities by ASD status, we found no significant differences in the risk of in-hospital mortality.

Our findings of higher risk of in-hospital mortality among adults with ASD mirror results from previous mortality studies (Bilder et al., 2013; Gillberg et al., 2010; Hirvikoski et al., 2016; Mouridsen et al., 2008; Pickett et al., 2011; Shavelle & Strauss, 1998) with a few important distinctions. This study specifically examined the risk of death during hospital admissions among adults with ASD using the largest national hospital discharge records in the United States. Unlike our study, previous studies were prospective cohort studies that followed people with ASD over time by linking local or national patient registries and mortality registry data and examined risk of premature mortality among people with ASD in general and unrelated to in-hospital mortality. Finally, most of the previous studies in the United States are based on small samples and were representative at state level. Our study, however, included a sample of adults with ASD from the largest nationally representative hospital discharge records data in the United States (AHRQ, 2017). Thus, our analysis contributes to a still nascent literature on mortality in people with ASD by providing findings that are generalizable to inpatient hospitalizations at a national level.

We found that people with ASD who experienced in-hospital mortality were at a higher risk for 10 out of 27 select medical comorbidities compared to their counterparts from the general population. The largest gaps or clinically meaningful differences in medical comorbidities between people with and without ASD who experienced in-hospital mortality were identified for psychoses, other neurological disorders, hypothyroidism, rheumatoid arthritis collagen vascular diseases, paralysis, followed by obesity, valvular disease, deficiency anemias, fluid and electrolyte disorders, and diabetes without chronic complications. These findings are important, because preventing in-hospital mortality requires the recognition of medical comorbidities and the pursuit of diagnosis and treatment for these comorbidities. Adults with ASD have a higher likelihood of dependence on others to recognize, report, and pursue treatment for signs and symptoms of emerging illness such as these comorbidities. Communication barriers between people with ASD and health care professionals (Nicolaidis et al., 2015; Raymaker et al., 2017) present

Table 5. The odds ratios for medical comorbidities among adults with ASD and matched control groups who experienced in-hospital mortality, separately for females and males, United States, 2004–2014.

Medical comorbidities	ASD females		Control females		OR	95% CI	ASD males		Control males		OR	95% CI
	(n = 8465)		(n = 25,392)				(n = 25,772)		(n = 77,319)			
	Deaths		Deaths				Deaths		Deaths			
	N	%	N	%			N	%	N	%		
All deaths	143	100.0	137	100.0			319	100.0	830	100.0		
Congestive heart failure	17	11.9	25	18.2	2.04**	1.10–3.78	22	6.9	90	10.8	0.73	0.46–1.17
Valvular disease	<11	2.8	<11	3.7	2.40	0.64–8.94	12	3.8	21	2.5	1.71	0.84–3.49
Pulmonary circulation disease	<11	4.2	14	10.2	1.29	0.49–3.35	17	5.3	39	4.7	1.31	0.74–2.31
Peripheral vascular disease	<11	2.8	17	12.4	0.71	0.24–2.10	13	4.1	46	5.5	0.85	0.46–1.57
Paralysis	21	14.7	<11	5.1	9.02***	3.83–21.22	31	9.7	46	5.5	2.02***	1.28–3.19
Other neurological disorders	48	33.6	<11	5.8	18.09***	8.56–38.26	99	31.0	77	9.3	3.87***	2.87–5.21
Pulmonary circulation disease	<11	7.0	39	28.5	0.77	0.38–1.54	29	9.1	108	13.0	0.81	0.53–1.21
Diabetes w/o chronic complications	16	11.2	29	21.2	1.66	0.90–3.05	37	11.6	85	10.2	1.31	0.89–1.92
Diabetes w/ chronic complications	NA	NA	NA	NA	NA	NA	<11	1.9	26	3.1	0.69	0.28–1.68
Hypothyroidism	20	14.0	20	14.6	3.00***	1.62–5.59	41	12.9	21	2.5	5.87***	3.47–9.93
Renal failure	<11	7.0	24	17.5	1.25	0.60–2.62	29	9.1	99	11.9	0.88	0.58–1.33
Liver disease	<11	3.5	10	7.3	1.50	0.51–4.39	12	3.8	74	8.9	0.49**	0.26–0.90
Peptic ulcer disease and bleeding	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Acquired immune deficiency syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lymphoma	NA	NA	NA	NA	NA	NA	<11	1.3	14	1.7	0.86	0.28–2.60
Metastatic cancer	<11	3.5	13	9.5	1.15	0.41–3.24	13	4.1	74	8.9	0.53**	0.29–0.95
Solid tumor w/o metastasis	NA	NA	NA	NA	NA	NA	<11	2.8	17	2.0	1.59	0.71–3.56
Rheumatoid arthritis collagen vascular disease	<11	6.3	<11	4.4	4.50***	1.60–12.66	<11	0.6	<11	0.6	1.20	0.23–6.19
Coagulopathy	20	14.0	39	28.5	1.54	0.90–2.64	61	19.1	183	22.0	1.00	0.75–1.34
Obesity	14	9.8	16	11.7	2.63***	1.28–5.39	21	6.6	31	3.7	2.03**	1.17–3.54
Weight loss	22	15.4	23	16.8	2.87***	1.60–5.16	43	13.5	106	12.8	1.22	0.85–1.74
Fluid and electrolyte disorders	74	51.7	83	60.6	2.69***	1.96–3.68	188	58.9	403	48.6	1.40***	1.18–1.67
Chronic blood loss anemia	NA	NA	NA	NA	NA	NA	<11	0.9	<11	1.0	1.13	0.30–4.24
Deficiency anemias	28	19.6	25	18.2	3.37***	1.96–5.78	56	17.6	128	15.4	1.31*	0.96–1.80
Alcohol abuse	NA	NA	NA	NA	NA	NA	<11	0.6	92	11.1	0.07***	0.02–0.26
Drug abuse	<11	0.7	<11	5.1	0.43	0.05–3.48	<11	1.3	69	8.3	0.17***	0.06–0.48
Psychoses	22	15.4	<11	5.1	9.45***	4.04–22.13	32	10.0	17	2.0	5.65***	3.14–10.2
Depression	<11	4.9	14	10.2	1.50	0.61–3.72	11	3.4	36	4.3	0.92	0.47–1.80
Hypertension	22	15.4	60	43.8	1.10	0.67–1.79	68	21.3	217	26.1	0.94	0.72–1.23

Source: Healthcare Cost and Utilization Project, National Inpatient Sample (HCUP-NIS) data, 2004–2014.We summarized the specific underlying causes of deaths based on the Agency for Healthcare Research and Quality (AHRQ) Elixhauser Comorbidity Index (Elixhauser, Steiner, Harris, & Coffey, 1998). To maintain confidentiality, cells with <11 cases cannot be reported.
*** $p < 0.01$, ** $p < 0.05$, and * $p < 0.1$.

additional challenges to identification and treatment of these comorbidities.

Unfortunately, a convergent body of literature noted that, in general, people with ASD experience suboptimal health care quality compared to the general population, in part due to lack of ASD knowledge and training among physicians and nurses (Gardner, Suplee, & Jerome-D'Emilia, 2016; Heidgerken, Geffken, Modi, & Frakey, 2005; Nicolaidis & Raymaker, 2013; Piven & Rabins, 2011). For example, some of the medical comorbidities (e.g. psychosis, other neurological disorders) may not be ones that physicians are adequately trained on as they occur with lower frequency in the general population. Furthermore, these experiences are exacerbated by significant social, communication and behavioral challenges that are associated with ASD including lower income (Roux et al., 2013; Shattuck et al., 2012) isolation (Mazurek, 2014; Orsmond, Shattuck, Cooper, Sterzing, & Anderson, 2013; Shattuck, Orsmond, Wagner, & Cooper, 2011), poorer physical and mental health (Kalb et al., 2012; Khanna, Jariwala-Parikh, West-Strum, & Mahabaleshwarkar, 2014; Mandell et al., 2005; Nicolaidis et al., 2012), depression and anxiety (Stewart, Barnard, Pearson, Hasan, & O'Brien, 2006), and poorer cognitive and behavioral function (Cochran et al., 2013; Guinchat et al., 2015; Leyfer et al., 2006; Matson & Neal, 2009; Raz, Lerner-Geva, Leon, Chodick, & Gabis, 2013; United States Government Accountability Office, 2016; Vohra, Madhavan, & Sambamoorthi, 2016; White, Oswald, Ollendick, & Scahill, 2009). Given our study findings, there is a critical need to improve health care, public health, and social support service interventions and strategies to reduce in-hospital deaths among people with ASD and address medical comorbidities that can potentially be linked to in-hospital deaths. Namely, management and optimization of the most prevalent medical comorbidities that are associated with in-hospital mortality among people with ASD, including psychoses, neurological disorders, and others, should be a priority focus of strategies for improving health care, preventive interventions, and training efforts. Most importantly and similar to previous studies (Bilder et al., 2013; Gillberg et al., 2010; Mouridsen et al., 2008; Pickett et al., 2011; Shavelle et al., 2001), we also found that women with ASD had significantly higher risk, both, for in-hospital mortality and women who experienced in-hospital mortality also had higher risk for different medical comorbidities compared to other women in the general population as well as men with ASD. Thus, among people with ASD, women are the more vulnerable with elevated risk of in-hospital mortality and high burden of medical comorbidities.

Limitations

The study limitations warrant consideration. First, some HCUP-NIS data may have been miscoded. The researchers could not verify the accuracy of the coded outcomes. Furthermore, the use of ICD-9 codes to identify people with ASD may have limitations in accuracy. It is possible that some individuals with ASD did not have an ICD-9 code for ASD listed on the associated medical service claim for the hospital admission, especially if the primary diagnosis of the hospitalization was unrelated to autism (e.g. acute respiratory infection, etc.). Therefore, these claims only represent people who have been identified as having ASD and may miss some people with ASD who have not been diagnosed. Nevertheless, the process for extracting ASD codes has been validated and widely used (Bush et al., 2017; Leslie & Martin, 2007). Second, the unit of analysis was hospitalization rather than the individual; therefore, an individual might be represented multiple times in the data if he or she was admitted to a hospital more than once in a single calendar year. Furthermore, this unit of analysis precludes identification of complications that were treated in the hospital prior to in-hospital death. Third, this analysis is not able to include people who do not have access to medical care, which may be a differential factor across those with and without ASD, due to the nature of its design. Thus, the results can only be generalized to individuals who received care in an inpatient hospital setting, as the causes of mortality likely differ between people with and without access to health care. Fourth, lack of precision in income measures within the large units of geography limit our ability to assess socioeconomic status on an individual level. The household income included in this article is based on the median household income for patient's five-digit ZIP code. Fifth, this data source contains missing data; however, multiple imputations were employed for variables with missing data, consistent with best practices (Royston, 2011; Schenker et al., 2006). Fourth, causality cannot be established due to the cross-sectional nature of the data (Baron & Kenny, 1986). Future studies need to use longitudinal data to examine in-hospital mortality among people with ASD. Given the emphasis on health care and social services research on reducing avoidable or preventable in-hospital mortality, the use of longitudinal data would also shed light on potentially modifiable in-hospital mortality risk factors. Finally, some of medical comorbidities had wide CIs for some of the associations which indicate an imprecise estimation, primarily due to the small number of observations for outcomes of interest. Hence, the results should be treated with caution. Despite these limitations, this study is the first to investigate differences between adults with and without ASD in their risk of in-hospital mortality using a robust and nationally representative sample of hospital discharge records data.

Conclusion

Data on mortality and medical comorbidities are essential in identifying priorities and strategies for health care and social services interventions and monitoring their

effectiveness. Research on mortality among people with ASD is vital to ensure that health care procedures and preventive interventions are adapted to the unique needs of those with ASD. To the best of our knowledge, this is the first study on in-hospital mortality among adults with ASD in the United States. The results of this study identified a higher risk of in-hospital mortality among people with ASD. Our findings underscore the need for more research to develop better strategies for healthcare and service delivery to people with ASD.

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Note

1. In parentheses in italics are HCUP-NIS specific data element that was used to derive study population and study variables (e.g. *AGE; DXn; HOSP_BEDSIZE*).

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Appendix 1. Psychiatric conditions with ICD-9 codes.

Outcomes	ICD-9 diagnosis
Psychiatric conditions	
Alcohol abuse	305.00; 305.01; 305.02
Alcohol dependence	303.xx
Anxiety disorder	300.0x; 300.2x; 300.3x; 309.20; 309.21; 309.24; 309.81
Bipolar disorder	296.0x; 296.1x; 296.4x; 296.5x; 296.6x; 296.7x; 296.80; 296.81; 296.89; 296.9x; 301.13
Attention deficit disorders	314.xx
Dementia	290.xx; 780.93x
Depression	296.2x;296.3x;296.82;298.0x;300.4x;301.12; 309.0x;309.1x;309.28; 311.xx
Drug abuse	305.20; 305.21; 305.22; 305.30; 305.31; 305.32; 305.40; 305.41; 305.42; 305.50; 305.51; 305.52; 305.60; 305.61; 305.62; 305.70; 305.71; 305.72; 305.80; 305.81; 305.82; 305.83; 305.91; 305.92
Drug dependence	304.xx
Obsessive–compulsive disorder	300.3x
Other psychoses	297.1x; 297.3x; 298.8x; 298.9x; 301.22
Schizophrenic disorders	295.xx
Suicide attempts E950–E958	E950–E958

Source: Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) data, 2004–2014.
ICD-9: International Classification of Diseases and Related Health Problems, 9th Revision.