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Mortality of Children with Autism Spectrum Disorder Using Data from a Large-Scale Korean National Cohort

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Purpose: This study aimed to investigate the association between autism spectrum disorder (ASD) diagnosis and mortality among children using the data from a large-scale national cohort of Korean infants and children. We also explored the association between hearing impairment detected during early infancy and mortality.

Materials and Methods: We performed a retrospective cohort study using the nationwide claims data of the Republic of Korea. Children born between 2007 and 2014 (n=3598904) were followed up until 2020. Cox proportional hazard models were used to examine the association between ASD diagnosis and mortality among children. Then, in order to evaluate the association between hearing impairment and mortality, Cox proportional hazard models were built using the responses related to hearing impairment asked during the first health screening (at age 4–6 months).

Results: Of the 3598904 children born between 2007 and 2014, 32878 children (0.9%) were diagnosed with ASD until the end of 2020. We identified that ASD diagnosis was associated with higher mortality among children [hazard ratio (HR)=2.5, 95% confidence interval (CI): 2.2–2.9]. This association was stronger among girls (HR=4.8, 95% CI: 3.9–5.8) compared to boys (HR=1.9, 95% CI: 1.6–2.2). We found that hearing impairment detected during infancy was associated with higher mortality among children with ASD diagnosis.

Conclusion: ASD diagnosis was associated with higher mortality among Korean children. This association was stronger in girls than in boys. Hearing impairment detected during infancy was also associated with higher mortality among children diagnosed with ASD.

Key Words: Autism spectrum disorder, mortality, hearing impairment, children, Republic of Korea

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and interaction, restricted interests, and repetitive behaviors.[1] Additionally, ASD is considered to be one of the leading causes of disability in children.[2,3] The prevalence of ASD is estimated to be 1.9% in the United States[4] and 2.6% in the Republic of Korea.[5]

Previous studies have reported that adult ASD patients have increased mortality, possibly due to comorbidities associated with the condition, such as epilepsy, as well as intentional and unintentional self-inflicted injuries.[6-8] However, there are limited studies on population-level analyses regarding pre-adults, especially children. Furthermore, it remains unknown whether children with ASD are at a higher predisposition of increased mortality. Meanwhile, recent studies have identified that children with ASD are likely to have hearing impairment from infancy.[1,9] These findings on the associated hearing impairments,

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in turn, have promoted the early detection of ASD in children, due to the detection of impaired sensory perception from the test conducted during infancy. However, although hearing impairment during infancy has been associated with various adverse health outcomes in the general populations,[10,11] it remains unclear and uninvestigated whether disease prognosis may differ between ASD children with hearing impairment and those without hearing impairment.

Therefore, given the aforementioned gaps in knowledge and limitations of prior studies, we performed longitudinal analyses investigating the association between ASD diagnosis and mortality among children using the data from a large-scale national cohort of Korean infants and children. We also explored the association between hearing impairment detected during infancy and mortality, as a proxy for prognosis, among children diagnosed with ASD.

MATERIALS AND METHODS

Study population

The National Health Insurance Service (NHIS) constructed a sample using their data from nationwide claims of health insurance and screening of all citizens in the Republic of Korea. We performed a retrospective cohort study using this nationwide claims data of health insurance and screening, which provides extensive information regarding demographics, socioeconomic status, medical service use, and mortality. To construct the study cohort, all children born between January 1, 2007 and December 31, 2014 were followed up until December 31, 2020. For the analyses on the association between hearing impairment and mortality, any children with an incomplete or missing information on the first health screening (4–6 months of age) were further excluded, since the developmental screening test, such as the early hearing detection test, starts from 4–6 months of age.

The Institutional Review Board (IRB) of Seoul National University Hospital approved the study protocol (IRB no. E-1909-095-1065) and waived the requirement of informed consent, since anonymized claims data was used.

Definition of autism spectrum disorder

We defined ASD through the identification of one of the following International Classification of Diseases-10 (ICD-10) codes recorded in the primary or secondary diagnosis found up to December 31, 2020: F84.0, F84.1, F84.5, F88.8, or F88.9. In the Korean context, the diagnosis of ASD is mostly made by a psychiatrist. This definition of ASD is consistent with previous studies assessing epidemiological features, and the prevalence was found to be comparable to or lower than those reported in previous studies.[5,12,13]

Assessment of hearing impairment

We assessed hearing impairment during infancy using the information on parental responses to the following question included in the first health screening (4–6 months of age): "Does your child respond to new sounds?"

Determination of mortality

We determined the mortality status and date of death using the death records included in the eligibility database of the NHIS data.

Statistical analysis

We constructed Cox proportional hazard models to examine the association between ASD diagnosis and mortality among children. As in previous studies, analytical models were adjusted for the birth year and household income and were stratified by sex to control possible confounding effects.[8] We assigned time at risk as the time from birth date to death date (for those who died during the study period) or December 31, 2020 (for those who were alive by the end of the study), since the diagnosis of ASD can be interpreted as a detection of early features of ASD, affected largely by genes and in-utero environments, rather than the onset of disease. We also stratified analyses by sex and hearing impairment status, based on the response to the question related to hearing impairment. Analytical models for hearing impairment-stratified analyses were only adjusted for household income with a stratification variable of sex, due to the problem of model convergence occurring from the small sample size of the strata of children with hearing impairment.

To evaluate the association between hearing impairment and mortality among children with ASD, we built separate Cox proportional hazard models using the responses to the question related to hearing impairment as an independent variable. These analytical models were also adjusted for the birth year and household income and were stratified by sex; and time at risk was assigned as the time from birth date to death date (for those who died during the study period) or December 31, 2020 (for those who were alive by the end of the study), since the number of acquired late onset hearing impairment cases was assessed to be negligible in this study identifying hearing impairment in children aged 4–6 months.[14]

RESULTS

Table 1 describes the study population, which was followed up until the end of 2020. Of the 3598904 children born between 2007 and 2014, 32878 children (0.9%) were diagnosed with ASD as of 2020. Of those subjects, 24459 (74.4%) were boys and 8419 (25.6%) were girls. Children with ASD were more likely to have hearing impairment (0.9%) than those without ASD (0.4%) (Table 1). Children born earlier during the study period or with lower household income were less likely to participate in the

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Table 1. Sociodemographic Characteristics of Children Included in the Analyses, Stratified by ASD Diagnosis

Characteristics	Total (n=3598904)	Children not diagnosed with ASD (n=3566026)	Children diagnosed with ASD (n=32878)	*p* value
Birth year				<0.001
2007	481425 (13.4)	477330 (13.4)	4095 (12.5)	
2008	454636 (12.6)	450741 (12.6)	3895 (11.8)	
2009	430082 (11.9)	426181 (11.9)	3901 (11.9)	
2010	453177 (12.6)	448736 (12.6)	4441 (13.5)	
2011	456078 (12.7)	451581 (12.7)	4497 (13.7)	
2012	470374 (13.1)	465955 (13.1)	4419 (13.4)	
2013	425805 (11.8)	421936 (11.8)	3869 (11.8)	
2014	427327 (11.9)	423566 (11.9)	3761 (11.4)	
Sex				<0.001
Boys	1850801 (51.4)	1826342 (51.2)	24459 (74.4)	
Girls	1748103 (48.6)	1739684 (48.8)	8419 (25.6)	
Household income				<0.001
High (15–20 ventile)	1269815 (35.3)	1258056 (35.3)	11759 (35.8)	
Middle (7–14 ventile)	1807260 (50.2)	1791393 (50.2)	15867 (48.2)	
Low (0–6 ventile)	521829 (14.5)	516577 (14.5)	5252 (16.0)	
Hearing impairment detected at 4–6 months of age				<0.001
No	2015515 (99.6)	1997912 (99.6)	17603 (99.1)	
Yes	8348 (0.4)	8181 (0.4)	167 (0.9)	

ASD, autism spectrum disorder.
Data are presented as a n (%).

Table 2. Associations between ASD Diagnosis and Mortality among Children

	Events/Person-years	HR	95% CI
Crude model			
No ASD	9843/35843066	Ref.	Ref.
ASD	237/328036	2.6	2.3–3.0
Adjusted model			
Total*			
No ASD	9843/35843066	Ref.	Ref.
ASD	237/328036	2.5	2.2–2.9
Boys†			
No ASD	5497/18362512	Ref.	Ref.
ASD	137/243852	1.9	1.6–2.2
Girls†			
No ASD	4346/17480553	Ref.	Ref.
ASD	100/84184	4.8	3.9–5.8

HR, hazard ratio; CI, confidence interval; ASD, autism spectrum disorder; Ref., reference.
*Estimated from Cox proportional hazard models stratified by sex and adjusted for birth year and household income, †Estimated from Cox proportional hazard models adjusted for birth year and household income.

Table 3. Association between Hearing Impairment Detected in Infancy (4–6 Months of Age) and Mortality among Children Diagnosed with Autism Spectrum Disorder*

Hearing impairment	Events/Person-years	HR	95% CI
Yes	67/166039	Ref.	Ref.
No	4/1578	5.8	2.1, 16.0

Ref., reference; HR, hazard ratio; CI, confidence interval.
*Estimated from Cox proportional hazard models stratified by sex and adjusted for birth year and household income.

first health screening (Supplementary Table 1, only online).

A total of 35843066 person-years were observed for children without ASD and 328036 person-years for those with ASD. The crude hazard ratio (HR) of mortality for children diagnosed with ASD compared to those without ASD was 2.6 [95% confidence interval (CI): 2.3–3.0]. After controlling for the abovementioned potential confounders (i.e., sex, household income, and birth year), the HR was 2.5 (95% CI: 2.2–2.9), slightly lower compared to the crude model (Supplementary Fig. 1, only online).

In the sex-stratified analyses, the HR was higher in girls (HR=4.8, 95% CI: 3.9–5.8) than in boys (HR=1.9, 95% CI: 1.6–2.2) (Table 2), showing a significant difference by sex (p<0.0001). The HRs for the association between ASD diagnosis and mortality were not different between children with hearing impairment (HR=4.3, 95% CI: 3.4–5.5) and those without (HR=4.3, 95% CI: 1.5–12.2).

Among children diagnosed with ASD (n=32878), hearing impairment detected during infancy was associated with a substantially higher risk of mortality (HR=5.8, 95% CI: 2.1–16.0) (Table 3 and Supplementary Fig. 2, only online).

DISCUSSION

In this study using a large-scale national cohort of Korean infants and children, we were able to identify an association be-

tween ASD and higher mortality among children. This association was stronger in girls than in boys. We also found that hearing impairment detected during infancy was associated with higher mortality among children diagnosed with ASD.

Given the current literature, the mean age of death for ASD patients was reported to be 36.2 years,[8] and previous studies investigating the association between ASD diagnosis and mortality were performed on adult populations only.[6-8] In these studies, ASD patients had a mortality rate that was 2 to 5 times higher than the general population due to comorbidities, such as epilepsy, as well as intentional and unintentional self-inflicted injuries.[6-8] To address the gaps in knowledge and limitations of prior studies, we observed an increased risk of mortality related to ASD among children, who generally have lower mortality risk than adults or the elderly. This interesting finding might be explained by the increased risk of injury (e.g., suffocation, asphyxiation, and drowning) or comorbid conditions[8,15] associated with ASD among children. However, due to insufficient data on the cause of death, this study was not able to pinpoint the reasons for the increased mortality observed in children. Further studies should aim to address such limitations and identify the causes of death to draw more specific public health implications (by investigating, for example, the association between ASD, hearing impairment, and traffic accident mortality).

The point estimates for the association between ASD diagnosis and mortality were larger among girls than among boys in the present study, which was consistent with previous findings among adults in Demark, Sweden, Australia, and the United States.[6,16-19] Although increased ASD mortality due to certain causes (e.g., injury) is more likely to occur in boys than in girls, the findings in the present study might be attributed to the fact that the general mortality risk is higher in boys than in girls, at least in part.[6] In addition, it might also be explained by the fact that more severe brain problems, such as comorbid epilepsy, are required for the typical ASD phenotype to be manifested in girls than in boys.[17] Since the reason for this sex-related difference is still unclear, further studies are needed to confirm the observed sex difference in the present study, especially with the information on the cause of death.

Sensory symptoms in the areas of hearing, vision, smell, and touch are prevalent in ASD patients, and can even appear during infancy.[20,21] Atypical sensory features may have detrimental cascading effects on social communication and reactivity,[21] and it was reported that sensory symptoms, such as reactivity, at 1 and 2 years of age are associated with ASD severity among preschool children.[20] Although we used simple hearing screening questions instead of a comprehensive evaluation of hearing, we found consistently increased risks of mortality for negative response to the question related to hearing impairment. These findings have important implications in public health regarding the significance of detecting sensory symptoms at the early stages of childhood, which would be clinically relevant in identifying priority groups for health intervention.

This study provides some new insights and evidence on the heightened risk of death in children with ASD. Moreover, the present study provides unique evidence on the association between hearing impairment during infancy and mortality among children with ASD. These results produced from a large-scale national cohort of Korean infants and children have substantial public health implications for planning future interventions and targeting priority groups.

However, this study has several limitations. First, the data sourced from the administrative claims-based cohort has inherent limitations. Although national health screening programs for all children began in 2008, the participation rate of children born between 2007 and 2014 in the first health screening was 56.2%, making it difficult for the results of this study to be generalizable (Supplementary Table 1, only online). Moreover, our results still undercount the true number of ASD cases, particularly due to missed diagnoses or untreated variables. Since the early diagnosis of ASD is difficult, the diagnostic codes are often inserted as other codes, such as ICD-10 codes R62.0 (delayed milestone), R62.8 (other lack of expected normal physiological development), and R62.9 (lack of expected normal physiological development, unspecified), instead of ICD-10 codes used in the present study to determine the outcome of interests (i.e., F84.0, F84.1, F84.5, F88.8, and F88.9). This possibility of outcome misclassification should be considered to interpret the results properly. Second, despite utilizing the national claims data, children in lower socioeconomic status households are less likely to visit a physician and seek treatment for ASD-related symptoms, which often leads to poor prognosis.[22,23] However, effect modification of the association between ASD diagnosis and mortality by income levels cannot be evaluated due to the limited power. Therefore, further studies should focus on expanding the sample size and number of variables. Third, although we controlled for sex, household income, and birth year in the present study, there remains a concern of residual confounding by factors, such as severe illnesses (e.g., cancer, congenital defects, and heart diseases). Therefore, studies considering potential confounders, especially severe illnesses, are warranted to confirm the observed association.

In conclusion, ASD diagnosis was associated with higher mortality among Korean children. Although the point estimate for the association were found to be larger among girls than among boys, this result should be interpreted with caution as the reason for this finding, in terms of the cause of death, is still unclear. Hearing impairment detected during infancy was also associated with higher mortality among children diagnosed with ASD. Ultimately, these results stress the importance of targeted public health interventions for children, namely the need to develop more robust programs for those diagnosed with ASD. This study also pinpoints the need to improve interventions for children detected with hearing impairments as early as infancy, which can be screened through simple and cost-effective clinical assessments.

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AUTHOR CONTRIBUTIONS

Conceptualization: Kyoung-Nam Kim, Sungchan Kang, Hyun Joo Kim, Jieun Yun, and Jin Yong Lee. Data curation: Kyoung-Nam Kim and Sungchan Kang. Formal analysis: Kyoung-Nam Kim and Sungchan Kang. Funding acquisition: Jin Yong Lee. Investigation: Kyoung-Nam Kim, Seung-Mi Yoo, Sungchan Kang, Hyun Joo Kim, and Jin Yong Lee. Methodology: Kyoung-Nam Kim, Sungchan Kang, and Jin Yong Lee. Project administration: Jieun Yun and Jin Yong Lee. Resources: Jieun Yun and Jin Yong Lee. Software: Kyoung-Nam Kim and Sungchan Kang. Supervision: Jin Yong Lee. Validation: Kyoung-Nam Kim and Sungchan Kang. Visualization: Kyoung-Nam Kim. Writing—original draft: Kyoung-Nam Kim and Seung-Mi Yoo. Writing—review & editing: Kyoung-Nam Kim, Seung-Mi Yoo, Sungchan Kang, Hyun Joo Kim, Jieun Yun, and Jin Yong Lee. Approval of final manuscript: all authors.

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