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Short communication

The co-occurrence of autistic spectrum disorder and schizophrenia: A nationwide population-based study

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ABSTRACT

Although the co-occurrence of autistic spectrum disorder (ASD) and schizophrenia have been previously reported, the scope and magnitude of this comorbidity across large samples have not been sufficiently established. This study was aimed to assess the co-occurrence between schizophrenia and ASD in a large dataset, and to examine its predominance across different age and sex groups. Schizophrenia patients and age and sex frequency controls (n = 49,334) were assessed for the prevalence of autism spectrum disorder. The sample was stratified by age and sex, and co-occurrence was assessed using univariate and multivariate logistic regressions. Results indicated that schizophrenia was associated with ASD (OR = 7.01, 95%CI 2.98–16.43, p < .0001) across all age groups aside from 50 to 70 years. This association was significant among male participants (OR = 11.69, 95%CI 3.59–38.01, p < .0001) but not among female participants (OR = 2.33, 95%CI 0.60–9.03, p = .21). These findings indicate a large overlap between schizophrenia and ASD, and point to the need to expand the understanding of the potential mediating mechanisms of this co-occurrence.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, characterized by persistent deficits in social communication and interaction, as well as restrictive and repetitive patterns of behaviors and activities (American Psychiatric Asso, 2013). With increasing frequency exceeding 1% of the population, an early childhood age of onset and severe disabilities and psychosocial burden, ASD is a growing significant public health concern (Burgha et al., 2016). Several co-occurring disorders have been found to be associated with ASD, nonetheless, one of the most compelling and severe disorders previously found to co-occur with ASD is schizophrenia (Marín et al., 2018). As both disorders are associated with significant functional and psychosocial deficits, their co-occurrence is considered highly impairing (Bechi et al., 2020). Therefore, efforts have been made in recent years to further capture the rates of co-occurrence.

Although early conceptualizations considered schizophrenia and ASD as one (Bender, 1947), these two disorders have been seen as mutually exclusive disorders over the past 50 years (American Psychiatric Asso, 2013). Nonetheless, several overlaps can be observed among these two co-occurring states. For example, it has been suggested that ASD and schizophrenia have a similar clinical presentation, such as social withdrawal, social cognition deficits, and negative symptoms (Esterberg et al., 2008). Moreover, genetic studies demonstrate several shared genetic factors, such as variations of DNA sequence in the genome (copy number variations, CNVs) and specific rare alleles (Lionel et al., 2013). It has also been suggested that ASD and schizophrenia share specific brain structure abnormalities, such as similar abnormal development in the striatum and frontal lobe, and similar reductions of gray matter volume in the limbic-striatal-thalamic circuit (Toal et al., 2009a). These shared mechanisms suggest the idea that these two conditions are related and perhaps even share a common psychopathology (Wood, 2017).

Although the notion that schizophrenia and ASD co-occur at a high

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rate has been previously suggested (Padgett et al., 2010), studies examining this specific co-occurrence are scarce. Chang et al. (Tzur Bitan et al., 2019) estimated the prevalence of ASD among 660 adult psychiatric outpatients with various psychiatric conditions by utilizing physician-administered screening questionnaires, and found a prevalence of 0.6%. Nonetheless, these patients were not exclusively diagnosed with schizophrenia (Chang et al., 2003). Hallerback et al. (2012) examined ASD occurrence among schizophrenia patients in a face-to-face psychiatric examination, and found a 60% co-occurrence in a small uncontrolled sample of 46 patients (Hallerback et al., 2012). Mandell et al. (2012) examined chart review, and performed clinical interviews integrated with social responsiveness scale to assess ASD prevalence, and found a 10% prevalence of ASD among 141 inpatients with various psychiatric diagnoses, yet utilized an uncontrolled population with a small sample (Mandell et al., 2012). Other studies (Sporn et al., 2004; Fraser et al., 2012; Waris et al., 2013) also employed a relatively small sample size, and most of them were uncontrolled. Thus, additional studies are needed in order to establish whether this co-occurrence is significant in rate and prevalence.

In this study, we aimed to assess the co-occurrence of ASD and schizophrenia and the extent to which this co-occurrence is present across different age and sex groups, while utilizing the highly validated databases of Clalit Health Services (CHS), the largest health insurance organization in Israel.

2. Methods

2.1. Data source

The CHS is one of four operating healthcare organizations to provide healthcare for all citizens of Israel, and with a coverage of nearly five million citizens, which is over 50% of the country's population (Ministry of Health (Il) (2018). This coverage is obtained through 1,427 primary healthcare units and additional medical facilities throughout Israel. The CHS incorporates continuous real-time data into their comprehensive database. Data is collected from administrative computerized operating systems in medical institutes, hospital and primary care physicians' reports, as well as from pharmacies and medical care facilities. The diagnosis of schizophrenia underwent a process of validation in a previous study (Tzur Bitan et al., 2019). For the purposes of the current study, the diagnosis of autism has undergone a similar process of validation. Author IK examined a random sample of 150 confirmed ASD cases and examined their registered diagnosis in the chronic registry of the CHS databases. Subsequently, 150 cases registered in the CHS databases were examined manually to assess the accuracy of diagnosis. Overall, a 93% accuracy rate was observed.

2.2. Study population and disease definition

The current database was composed of cases included in the CHS database as insured patients from the year 2000 and up until October 2017. Inclusion criteria included an age range of 18–70, and a diagnosis of schizophrenia. Matched cases were obtained at a 1:1 ratio and were sex and age frequency matched, and comprised random cases from the population of CHS-insured citizens. Diagnoses of autism and schizophrenia were based on the diagnosis registration of either a community psychiatrist or documentation on a discharge letter from a mental health hospital. A diagnosis of schizophrenia was based on code 295 of the ICD-9 (schizophrenia) which includes the following subtypes: paranoid, disorganized, catatonic, simple and paranoid type; acute schizophrenic episode; latent, residual schizophrenia and unspecified schizophrenia; schizoaffective disorder. A diagnosis of autism spectrum disorder was based on codes 299 and F84 of the ICD-9 and 10 (pervasive developmental disorders) which include the following subtypes: infantile autism (current or active state), disintegrative psychosis, other specified early childhood psychosis, unspecified childhood psychosis, pervasive developmental disorder, childhood autism, atypical autism, Rett syndrome, Asperger's syndrome, other pervasive developmental disorders, and pervasive developmental disorder unspecified. Prior estimates of prevalence for ASD indicated that the cumulative incidence of ASD in a population of 8-year-old children in Israel was 0.49% (1 in 203) (Raz et al., 2015), whereas crude prevalence rate of schizophrenia was found to be 3 per 1,000 (Kodesh et al., 2012). Demographic information included marital status, age, sex, ethnocultural sector, and socioeconomic status. The study was approved by the CHS institutional review board (IRB).

2.3. Statistical analysis

Differences in sociodemographic characteristics were assessed using chi-square and binary logistic regressions for categorical variables and t-tests for continuous variables. Univariate logistic regressions were employed to test the association between autism and schizophrenia, while stratifying to different age and sex groups. Statistical analysis was performed using SPSS software, version 25 (SPSS, Chicago, IL, U.S.A.), using a $p < .05$ threshold for statistical significance.

3. Results

3.1. Study participants

Significant differences were observed between the cohort of schizophrenia patients and their matched controls (Table 1). Compared to control cases, patients with schizophrenia were significantly more likely to be single (79.0%) and come from a low (47.7%) to medium (39.4%) socioeconomic status. Distribution of sectors also varied significantly, with fewer schizophrenia patients in the Arab sector. Overall, the majority of the sample came from the 30–49 and 50–70 age groups, with only 12% in the 18–29 age group. The mean age of schizophrenia diagnosis was 12.37 (SD = 9.72). The mean age of ASD diagnosis was 8.03 (SD = 11.31). Across the younger age groups, schizophrenia diagnoses was given at significantly older age compared to ASD diagnoses ($t(65) = 2.97$, $p < .01$; $t(76) = 2.16$, $p < .05$), respectively), with no significant differences in age of onset at the older age group ($t(7) = 1.00$, $p = .35$). The majority of the sample comprised male participants (63.1%).

A significant association between autism and schizophrenia (OR = 7.01, 95%CI 2.98–16.43, $p < .001$) was found (Table 2). This association was only significant in the 18–29 age group (OR = 6.03, 95%CI

Table 1
Sociodemographic and clinical characteristics of the study population.

	Schizophrenia (n = 24, 667)		Control (n = 24, 667)			
	n	%	n	%	χ^2	p-value
Age group						
18–29	2,969	12.0	2,969	12.0		
30–49	10,823	43.9	10,823	43.9		
50–70	10,875	44.1	10,875	44.1	N.A	N.A
Sex						
Male	15,561	63.1	15,561	63.1		
Female	9,106	36.9	9,106	36.9	N.A	N.A
Marital status						
Married	5,187	21.0	14,986	60.8		
Single	19,480	79.0	9,681	39.2	8052.61	.000
Sector						
General	19,334	78.4	17,769	72.0		
Arab	3,849	15.6	5,897	23.9		
Ultraorthodox Jews	1,484	6.0	1,001	4.1	590.25	.000
Socioeconomic Status						
Low	11,721	47.7	10,357	42.1		
Medium	9,686	39.4	8,977	36.5		
High	3,154	12.8	5,244	21.3	631.33	.000

Table 2
Prevalence, ORs, and significance of association between autism and schizophrenia, stratified by sex and age group.

	Schizophrenia	Controls	OR (95% CI)	p
	n (%)	n (%)		
All	42 (0.2%)	6 (0.0%)	**7.01 (2.98–16.43)**	**.000**
Age, years				
18–29	18 (0.6%)	3 (0.1%)	**6.03 (1.77–20.49)**	**.004**
30–49	21 (0.2%)	2 (0.0%)	**10.51 (2.46–44.87)**	**.001**
50–70	3 (0.0%)	1 (0.0%)	3.00 (.031–28.85)	.341
Sex				
Male	35 (0.2%)	3 (0.0%)	**11.69 (3.59–38.01)**	**.000**
Female	7 (0.1%)	3 (0.0%)	2.33 (0.60–9.03)	.219

1.77–20.49, $p < .01$) and the 30–49 age group (OR = 10.51 95%CI 2.46–44.87, $p < .01$). Stratification by age indicated that this association was significant and large among males (OR = 11.69, 95%CI 3.59–38.01, $p < .001$) but not significant among females (OR = 2.33, 95%CI 0.60–9.03, p = ns).

4. Discussion

Using the highly validated diagnostic data derived from the databases of CHS, we found the odds of ASD among schizophrenia patients to be significantly higher compared to the odds among control participants (OR 7.01). Furthermore, we found that this association was present only among the young age groups and among males, but not among females. Studies indicate that schizophrenia is most frequently diagnosed by late adolescence or in one's early twenties (Díaz-Caneja et al., 2015), while ASD is more frequently diagnosed by the age of 4 (Mandell et al., 2005). Furthermore, in a study assessing the effect of age and sex on ASD and comorbid conditions, it was found that the prevalence of schizophrenia among ASD patients increased with age, and affected larger proportion of older adult males (Supekar et al., 2017). These findings support the idea that the neurodevelopmental deficits of ASD may result in a risk for developing psychosis later in life (Toal et al., 2009b; Baron-Cohen, 2002). Another explanation to account for the increased co-occurrence in the two younger age groups is that ASD diagnosis rates are higher among patients born in the last decades (Raz et al., 2015). Future studies focusing on longitudinal assessment of the evolution of the schizophrenia-ASD comorbidity as a function of diagnosis rates may provide empirical examination of such possibility.

The co-occurrence of schizophrenia and ASD was found only among males and not among females. Studies indicate that men are much more prone to be affected by ASD than are women (Burgha et al., 2016). It has been previously suggested that the strong male bias in ASD prevalence is related to the dominance of testosterone, which leads to a "hypermasculinization of the brain." (Da Silva and Ravindran, 2015) Interestingly, studies have indicated that sex hormones may contribute to sex differences in schizophrenia as well, indicating that lower levels of estrogen are linked to higher symptom severity in schizophrenia (Díaz-Caneja et al., 2015). Thus, a potential explanation to account for our findings is that male ASD patients may represent a different genetic pathophysiological process (than that represented by female ASD patients) which may lie closer to the pathophysiological processes underlying schizophrenia. Such a mediational explanation should be subjected to future research.

The results of the study have several clinical and empirical implications. Establishing the co-occurrence of schizophrenia and ASD highlights the importance of designing relevant treatment programs while also examining the specific needs of patients with such a challenging comorbidity, which may routinely be overlooked. Establishing the co-occurrence of schizophrenia and ASD highlights the importance of designing new, personalized and integrated treatment programs for this complex condition. Furthermore, addressing the shared symptoms exhibited in both disorders, such as social cognition deficits and social withdrawal, could be a primary goal of treatment. Seeing that antipsychotics have been shown to be less effective in treating the negative symptoms of schizophrenia, alternative treatments may be more suitable for both diagnoses, for example cognitive remediation or theory of mind training (Bechi et al., 2020). Further research is required to delineate the shared etiology, pathophysiology, and psychopathology of schizophrenia and ASD, and to develop new protocols and evidence-based programs to advance healthcare services for this population.

This study has several strengths. The study utilized a matched controlled design which assessed a homogeneous sample of patients with schizophrenia. The diagnoses included in this study were validated both electronically and manually. The reliance on the databases of the CHS allowed for examination of the schizophrenia-ASD co-occurrence in a large sample size, as opposed to previous studies which utilized clinical interviews and employed small samples. Nonetheless, the use of ICD coded diagnoses may be at the expense of clinical accuracy, and although the diagnoses in this database has been validated and found to be 94% accurate, such difference may pose as a potential limitation. The ASD diagnosis in this study included the diagnoses of 'other specified early childhood psychosis' and 'unspecified childhood psychosis', which may indicate a potential overlap with childhood-onset schizophrenia. Nonetheless, these diagnoses were observed among 0.032% of the sample, therefore the possibility that this overlap explains the observed findings is unlikely. Future studies should assess the level of comorbidity within each subcategory, while assessing the proportion of comorbidity attributed to potential overlapping states. As the study utilized the medical diagnoses provided by clinicians, the possibility of sex bias, whereby females who meet the criteria for ASD do not receive the official clinical diagnosis, cannot be ruled out. Furthermore, it is possible that men affected by ASD exhibit more symptoms that resemble or even match schizophrenia symptoms, compared to those exhibited by women. These potentially competing explanations should be further examined so as to validate our findings. Notwithstanding these limitations, the results of the study provide essential empirical support for ASD and schizophrenia co-occurrence, needed to inform both clinical research and practice.

Author statement

Author IK designed the study, wrote the initial draft of the manuscript and critically revised the manuscript. Authors IK and AGG performed the literature review and critically revised the manuscript. Authors DC, OW and KK supervised and assisted with datamining procedures and critically revised the manuscript. Authors KK and DTB performed and reported on the statistical analyses and critically revised the manuscript.

Declaration of competing interest

The authors of this manuscript have no conflict of interest to declare with regards to this manuscript. Other financial relations are as follows: Prof. Arnon Cohen received research grants from Janssen, Novartis, AbbVie, Janssen and Sanofi. Prof. Arnon Cohen served as a consultant, advisor or speaker to AbbVie, Amgen, Boehringer Ingelheim, Dexcel pharma, Janssen, Kamedis, Lilly, Neopharm, Novartis, Perrigo, Pfizer, Rafa, Samsung Bioepis, Sanofi, Sirbal and Taro. Dr. Dana Tzur Bitan received a research grant from Pfizer. All other authors have no other financial relations to declare.

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