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ORIGINAL PAPER

COVID-19 Morbidity Among Individuals with Autistic Spectrum Disorder: A Matched Controlled Population-Based Study

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Abstract

In this study we aimed to assess whether individuals with ASD are prone to higher infection rates, or to severe COVID-19 illness. Individuals with ASD and age- and gender-matched controlled counterparts (total $n = 32{,}812$) were assessed for COVID-19 infection rates and hospitalizations. Results indicated higher infection rates among individuals with ASD, with the largest effect among individuals aged 40–60 (OR = 2.05, 95%CI 1.33–3.15, $p < .001$), as well as higher odds for hospitalizations, evident primarily in men (OR = 2.40, 95%CI 1.14–5.02, $p = 0.02$) but not women. Medical and environmental risk factors may associate ASD with higher infection and morbidity rates. Healthcare policy providers should consider proactive steps to protect this population from the associated risks.

Keywords Autism Spectrum Disorder · ASD · Population-based · COVID-19 · Infection · Morbidity

The ongoing spread of the coronavirus disease 19 (COVID-19) caused by SARS-CoV-2, has led to wide implications in different areas of public health, with some populations reporting more serious adverse effects of the pandemic then others. Older age, male sex, obesity, type 1 and type 2 diabetes, hypertension and other background diseases have all been associated with greater morbidity (Zhou et al., 2021; Li et al., 2020), and vulnerable groups which tend to suffer from these conditions have previously demonstrated a more severe outcome (Tzur Bitan et al., 2021). As vaccination efforts are spreading worldwide, one of the challenges facing the medical community is to identify vulnerable groups which are more susceptible to significant morbidity, so as to focus prevention efforts on these populations. Along these lines, recent guidelines for vaccinations in Israel have suggested that children with neurodevelopmental disorders may constitute such a risk group, and therefore should be allowed to be vaccinated even by ages of 12–16 (Ministry of Health, 2021). Nonetheless, not much is known about the infection and morbidity rates of individuals with ASD thus far.

Characterized by persistent deficits in social communication and interaction (APA, 2013), Autistic Spectrum Disorder (ASD) is considered one of the most frequent neurodevelopmental disorders, with estimated prevalence of 1.6% in children at the age of 8 in the US (Christensen et al., 2019). With the emergence of the COVID-19 pandemic, scholars have suggested that individuals with ASD are especially prone to suffer from physical comorbidities known to serve as risk factors for COVID-19 morbidity, and are more likely to be infected due to their difficulty to adjust to social distancing and hygiene routines (Eshraghi et al., 2020). Furthermore, it has been suggested that increases of inflammatory cytokines and abnormal immune responses, known to characterize ASD pathophysiology, may cause increased risk for potential cytokine storm, one of the main inflammation mechanisms of COVID-19 (de Sousa et al., 2020). Although such hypotheses are compelling, to the best of our knowledge no study have previously demonstrated an

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association between ASD and COVID-19 morbidity. This study was aimed to bridge this gap in literature.

In this study we aimed to assess the prevalence of COVID-19 infection rates, as well as COVID-19 significant morbidity as identified by hospitalizations, among ASD individuals and compared to their age and gender matched controlled counterparts. We aimed to assess whether infection and hospitalization rates differed among the groups, and whether these differences are present in different age groups and across male and female participants. Finally, we aimed to assess whether the association of ASD and COVID-19 morbidity remains after controlling for potential risk factors such as diabetes, asthma, hypertension and obesity. The study employed the databases of Clalit Health Services in Israel, the largest healthcare organization insuring approximately 60% of Israel's population (Ministry of Health, 2018).

Methods

Data Source

The Clalit Health Organization (CHS) is the largest operating healthcare organization in Israel, and is one of four operating healthcare organizations insuring all citizens of Israel. The databases of the CHS are updated regularly by incoming information from medical care facilities and hospitals, pharmacies, and administrative medical operating systems. The CHS registry was previously validated by the founders of its algorithms (Rennert & Peterburg, 2001), as well as by many other authors utilizing the database (Friedman et al., 2018; Krieger et al., 2019; Reges et al., 2020; Shalom et al., 2018).

Data for the current study was mined on February 11, 2021. A total of 16,779 individuals with ASD diagnosis were retrieved. Of them, 246 individuals were excluded due to insufficient data, thus resulting in a sample of 16,532 individuals with ASD and their matched controls (total $n = 33{,}064$). Additional 126 cases were deceased and therefore removed along with their matched counterparts, thus resulting in a total of 32,812 cases. Thus, a total of 32,812 were analyzed. The study was approved by the approved by the CHS institutional review board (IRB, approval number 0022-16). Informed consent was waived due to the nature of data extraction.

Disease Definition

The diagnosis of ASD in the CHS databases is based on 299 and F84 codes of the 9th and 10th versions of the ICD, and include infantile autism, 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. The diagnosis was previously manually validated (Krieger et al., 2021), and was found to present a 93% accuracy. Diagnosis of ASD in Israel is typically made by a clinical interview aimed as assessing the presence of the main diagnostic criteria of the ICD or DSM. In some cases, patients' families, teachers and educational counselors may be requested to fill out assessment tools, and patients may undergo further examinations using additional validated diagnostic measures, in order to assist with the provision of an accurate diagnosis. Demographic variables extracted for this study included age, gender, and country of birth, while clinical variables include diabetes, asthma, hypertension, and obesity. COVID-19 infection indicators include rates of positive results. Hospitalizations were defined as admissions to a COVID-19 hospital ward specifically aimed to treat COVID-19 complications.

Study Participants

Table 1 presents the demographic characteristics of the ASD and control groups, along with significance of differences between them.

The mean age of the ASD and control group was 14.39 (SD = 10.29), with the majority of cohort being at the age group of 0–16. Significant differences were observed in country of birth and clinical factors, these differences were

Table 1 Demographic and clinical characteristics of the study sample ($n = 32{,}812$)

	ASD ($n = 16{,}406$)	Control ($n = 16{,}406$)	
Age	14.39 (10.29)	14.39 (10.29)	
Age groups			
0–15.9	10,866 (66.2%)	10,866 (66.2%)	N/a
16–20.9	2320 (14.1%)	2320 (14.1%)	
21–39.9	2662 (16.2%)	2662 (16.2%)	
40–59.9	500 (3.0%)	500 (3.0%)	
60 +	58 (0.4%)	58 (0.4%)	
Gender			
Male	13,196 (80.4%)	13,196 (80.4%)	N/a
Female	3210 (19.6%)	3210 (19.6%)	
Country of birth			
Israel	15,584 (95.0%)	15,843 (96.6%)	**<.001**
Else	808 (4.9%)	549 (3.3%)	
Unknown	14 (0.1%)	14 (0.1%)	
Diabetes	51 (0.3%)	196 (1.2%)	**<.001**
Asthma	876 (5.3%)	1372 (8.4%)	**<.001**
Hypertension	59 (0.4%)	225 (1.4%)	**<.001**
Obesity	3474 (21.2%)	2245 (13.7%)	**<.001**

Values marked in Bold indicate significance level of <.05.

adjusted in subsequent analyses and included differences in country of birth ($\chi^2(1) = 51.56$, $p < 0.001$), diabetes ($\chi^2(1) = 85.76$, $p < 0.001$), asthma ($\chi^2(1) = 117.48$, $p < 0.001$), hypertension ($\chi^2(1) = 97.87$, $p < 0.001$), and obesity ($\chi^2(1) = 319.86$, $p < 0.001$). These differences indicated that ASD individuals are less likely to be Israeli born, and are also less likely to suffer from asthma, diabetes and hypertension. On the other hand, they were more likely to suffer from obesity.

Statistical Analyses

Significance of differences in demographic and clinical factors among the two study groups were assessed using chi-square and binary logistic regressions for categorical variables and t-tests for continuous variables. Univariate logistic regressions were utilized to determine the association between ASD and COVID-19 infection and morbidity rates while stratifying the sample into age and gender groups. To assess the association between ASD and COVID-19 morbidity after controlling for known risk factors, multivariate logistic regression was employed, and odds ratio (OR) and 95% confidence intervals (CI's) were reported. All statistical analysis were performed with SPSS software, version 25 (SPSS, Chicago, IL, U.S.A.), with a threshold of $p < 0.05$ for statistical significance.

Results

Table 2 presents the overall infection rates, as well as infection rates stratified by age and sex.

As can be seen, higher infection rates were observed among the ASD group (OR = 1.16, 95%CI 1.07–1.27, $p < 0.001$), with differences reaching significance in the age group of 0–16 (OR = 1.31, 95%CI 1.17–1.47, $p < 0.001$) and 40–60 (OR = 2.05, 95%CI 1.33–3.15, $p = 0.001$). Differences in infection rates between ASD and controls were significant among men (OR = 1.19, 95%CI 1.08–1.31, $p < 0.001$) but not women. Additional exploratory analyses aimed to evaluate whether there are sex differences within the 40–60 age group indicated significantly higher rates of infection among male

Table 2 COVID-19 infection rates among ASD and controls, stratified by age and gender

	ASD ($n = 16{,}406$)	Controls ($n = 16{,}406$)	OR	95% CI		p
				Lower	Upper	
Overall infection rate (% positive)	1172 (7.1%)	1014 (6.2%)	**1.16**	**1.07**	**1.27**	**<.001**
Infection by age groups						
0–16	683 (6.3%)	527 (4.8%)	**1.31**	**1.17**	**1.47**	**<.001**
16–21	180 (7.8%)	207 (8.9%)	0.85	0.69	1.05	.15
21–40	240 (9.0%)	240 (9.0%)	1.00	0.82	1.20	1.00
40–60	67 (13.4%)	35 (7.0%)	**2.05**	**1.33**	**3.15**	**<.001**
60 +	2 (3.4%)	5 (8.6%)	0.37	0.07	2.03	.25
Infection by gender						
Male	949 (7.2%)	804 (6.1%)	**1.19**	**1.08**	**1.31**	**<.001**
Female	223 (6.9%)	210 (6.5%)	1.06	0.87	1.29	.51

Values marked in Bold indicate significance level of <.05.

Table 3 Hospitalization rates among ASD and controls, stratified by age and gender

	ASD ($n = 16{,}406$)	Controls ($n = 16{,}406$)	OR	95% CI		*p*
				Lower	Upper	
Overall hospitalization rate (%hospitalized)	29 (0.2%)	15 (0.1%)	**1.93**	**1.03**	**3.61**	**.038**
Hospitalization by age groups						
0–16	7 (0.06%)	5 (0.04%)	1.40	0.44	4.41	.56
Else	22 (0.39%)	10 (0.18%)	**2.20**	**1.04**	**4.66**	**.038**
Hospitalization by gender						
Male	24 (0.18%)	10 (0.07%)	**2.40**	**1.14**	**5.02**	**0.02**
Female	5 (0.15%)	5 (0.15%)	1.00	0.28	3.45	1.00

Values marked in Bold indicate significance level of <.05.

individuals with ASD (χ^2 (1) = 9.07, $p < 0.01$) whereas no such differences were detected across female participants in the same age group (χ^2(1) = 2.29, $p = 0.13$).

Table 3 presents the hospitalization rates among ASD and control group, stratified by age and gender.

As can be seen, ASD patients had higher odds for hospitalization (OR = 1.93, 95%CI 1.03–3.61, $p = 0.038$), which were observed only at ages of above 16 (OR = 2.20, 95%CI 1.04–4.66, $p = 0.03$). Hospitalizations rates differed only among man (OR = 2.40, 95%CI 1.14–5.02, $p = 0.02$), with ASD male individuals showing higher prevalence of hospitalization. These differences were not observed in women.

Table 4 presents the association between ASD and infection rates while controlling for the significant demographic and clinical factors.

ASD continued to be a significant predictor for infection rates after controlling for all medical and demographic factors (OR = 1.14, 95%CI 1.05–1.25, $p = 0.02$), with obesity being a second significant predictor with roughly the same levels of significance (OR = 1.17, 95%CI 1.05–1.31, $p = 0.04$). Due to the small number of hospitalized individuals in the current cohort ($n = 44$), a model adjusting for all risk factors would result in unstable estimates, therefore we adjusted only for obesity. The model resulted in a significant association between ASD and hospitalization, even after controlling for obesity (OR = 1.96, 95%CI 1.04–3.66, $p = 0.03$), while obesity became non-significant (OR = 0.82, 95%CI 0.36–1.85, $p = 0.82$).

Discussion

This study was aimed to assess COVID-19 infection and morbidity rates among individuals with ASD, as compared to individuals with no ASD which were matched by age and gender. The results indicated of substantial differences in infection rates between ASD and controls evident in the age group of 40–60 years old, followed by the 0–16 age group. Furthermore, we found that these differences were significant among male ASD individuals, but not among females. Hospitalization rates also differed across the two groups, with higher hospitalization rates observed in ASD individuals compared to controls. These differences were significant only above the age of 16 and among male individuals. Finally, we found that infection and hospitalization rates differed even after controlling for clinical risk factors, although information on hospitalization rates was restricted to control only for obesity, due to the relatively small number of hospitalized patients.

Consistent with previous reports expressing concerns of higher infection rates among individuals with ASD (Eshraghi et al., 2020), the results of the study confirm that overall, individuals with ASD have increased risk for COVID-19 infection, as indicated by 7.1% of individuals with ASD found positive for COVID-19, compared with 6.2% among controls. Eshraghi et al. (2020) previously suggested that behavioral challenges such as deficits in social communication, irritability, and aggression, may result in difficulty in maintaining physical distancing and adjusting to the COVID-19 routines. This explanation may account for the higher rates of infection found in this study. The results indicating of significant differences in the ages of 0–16 may be associated with the infection rates in educational systems, as previous literature highlighted the role of schools in increasing the risk of infection (Gurdasani et al., 2021) as well as the risk for virus transition into households (Lessler et al., 2021). Furthermore, ages of 40–60 are associated with more frequent social or familial interactions, which may result in higher infection rates (Qian et al., 2020). Such potential explanatory routes require additional investigation.

Once infected, ASD patients were significantly more prone to severe COVID-19 illness, as indicated by higher hospitalization rates, compared to controls. These results are likely to be associated with the observed higher rates of chronic diseases among this population, which are all known to cause COVID-19 complications. The fact that these differences were significant only at the ages of above 16 provide further support for the hypothesized effect of clinical risk factors, as some of the clinical factors such as diabetes and hypertension are more evident in adults (Geldsetzer et al., 2018). An additional competing explanation is related to changes in the immune system of ASD patients. Studies indicate that individuals with ASD have increased inflammatory cytokines, and are prone to changes in the immune response to different pathogens. Specifically, it was reported that ASD patients have pathologic changes in the activation profile of T cells which are assumed to modulate behavior (Ashwood et al., 2011), and that CNS

Table 4 Association between infection rates and ASD while controlling for medical risk factors

Predictors	Odds for infection rates			
	OR	95% CI		*P*
		Lower	Upper	
Country of Birth	0.95	0.76	1.19	.68
Diabetes	0.90	0.52	1.56	.71
Asthma	0.93	0.78	1.11	.46
Hypertension	0.89	0.53	1.49	.66
Obesity	**1.17**	**1.05**	**1.31**	**.004**
Autism	**1.14**	**1.05**	**1.25**	**.002**

Results of a multivariate logistic regression assessing the odds of infection for a given predictor, with each predictor assessed for its unique contribution after all other factors are controlled

Values marked in Bold indicate significance level of <.05.

neurons respond to IFN-gama derived from T cells to produce an elevation of tonic GABAergic inhibition (Filiano et al., 2016). These pro-inflammatory cytokines were previously demonstrated to be pathologically high among COVID-19 patients with acute respiratory distress syndrome (Conti et al., 2020). Thus, it is possible that ASD individuals are especially prone to higher COVID-19 morbidity because of this shared underlying immunologic basis. Such a hypothesis should be evaluated in future research.

Gender differences were found in both infection and hospitalization rates, indicating that male ASD participants had higher rates of both infections and hospitalizations. This finding is consistent with previous literature (Peckham et al., 2020; Vahidy et al., 2021) which generally demonstrated higher COVID-19 hospitalization and infection rates in male subjects. It has been suggested that sex differences in the immune system explain the differences between the sexes in COVID-19. Studies reporting of gender differences in COVID-19 infection and hospitalization rates suggest that female immune system has a more robust response to COVID-19 because of a more prominent production of INF-alpha compared to males (Peckham et al., 2020). Thus, it is possible that male ASD participants are more immunologically vulnerable to COVID-19, while female ASD patients share the same robust immunological response.

The findings reported in the current study have several important clinical and empirical implications. The results suggestive of increased risk for COVID-19 infections and hospitalizations among ASD patients may lay the grounds for future research examining shared immunologic deficits in ASD and COVID-19. Such line of investigation may first require more robust designs aimed to control for behavioral and immunological variables. Although significant differences in infection rates were observed, these differences were relatively modest across the entire sample, and are larger primarily in specific age groups. Future studies may focus on these groups and the reasons leading to the observed associations among them. Future research should also concentrate on environmental and biological mediating mechanisms which might account for the high COVID-19 morbidity. Clinically, the results highlight the importance of prevention efforts among this highly vulnerable group of patients, and suggests that ASD patients should be prioritized for vaccinations even at ages lower than 16, as recommended in Israel.

The current study has several strengths, which include a large sample size allowing for adequate statistical power, the utilization of a validated database, and the methodological design of a matched controlled cohort. Nonetheless, several limitations also exist. This study reports on the association between ASD and higher infection and hospitalization rates, yet did not assess the reasons for these associations. Additional studies are needed to explore several potential underlying mechanisms leading to the observed findings. For example, reduced mask wearing, or social and behavioral factors associated with ASD, may have led to increased rate of infection among this population. Factors related to changes in the immune system may explain the higher hospitalization rates. Such explanatory routes should be subjected to future research. Future studies should also explore whether infection rates are associated with ASD severity. Since this study is epidemiological in nature, no clinically validated measure was utilized, and the diagnoses rely on the clinical impression of an expert psychiatrist. Future studies should assess whether these results replicate while utilizing different assessment measures. Additional studies should further explore the effect of gastrointestinal dysfunctions on the observed associations, in light of their role in inflammatory alterations. The presented data is based on Israeli databases, hence—there may be cross-cultural differences when compared with different cultures and countries. Moreover, as different governmental policies were employed to reduce infection rates in different countries, results may differ as a function of extent of lockdowns or level of governmental policy rigorousness. Finally, as the vaccination plan of Israel was launched at the end of December 2020, it is possible that infection rates were influenced by the rates of vaccinations. As the dataset was mined approximately a month and a half after the launch of the plan, and full vaccination requires at least three weeks between vaccination shots, the influence of the spread of vaccination on the reported results is likely to be minimal. Notwithstanding these limitations, the results of this study bare important implications for both researchers and clinicians, and can inform policy makers dealing with prevention of COVID-19 morbidity worldwide.

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Declarations

Conflict of 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 and from the American Psychological Foundation. All other authors have no conflict of interests to declare.

Ethical Approval The study was approved by the approved by the institutional review board of the organization conducting the study (IRB, Approval Number 0022-16).

Informed Consent Informed consent was waived due to the nature of data extraction.

Research Involving Human Participants and/or Animals The study was approved by the approved by the Clalit Health Services institutional review board (IRB, approval number 0022-16). Informed consent was waived due to the nature of data extraction.

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