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Comparative Analysis of COVID-19 Severity and Mortality Among Vaccinated and Unvaccinated Individuals During the Delta Variant Surge in a Tertiary Care Center: A Cohort Study

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ABSTRACT

Background and Aims: On March 11, 2020, the World Health Organization declared Coronavirus disease 2019 (COVID-19) as a pandemic. The spread of the Delta variant of coronavirus started in June 2021 and accounted for the fifth peak of COVID-19 in Iran in July 2021. According to reports from other countries, vaccination protects against severe diseases caused by COVID-19, including the Delta variant. Studies have also shown that vaccination provides strong protection against SARS-CoV-2 infection, COVID-19-related hospitalization, and mortality. This retrospective cohort study was designed based on the medical care monitoring center database of Sayyad Shirazi Hospital.

Methods: COVID-19 confirmed patients' data were extracted for this study from June 22, 2021, to September 22, 2021 including demographic characteristics, signs and symptoms, ICU admission, need for aggressive oxygen therapy, including intubation, mortality, and vaccination status.

Results: A total of 2962 patients were enrolled. Being vaccinated was associated with a 4.14-fold increase in survival (adjusted OR = 4.14; 95% CI: 2.22–7.69; $p < 0.01$), and individuals in a younger age group demonstrated a 5.58-fold higher likelihood of surviving (adjusted OR = 5.58; 95% CI: 4.25–8.14; $p < 0.01$). The risk of severe COVID-19 was significantly lower in vaccinated individuals, showing a 3.12-fold decrease in risk (adjusted OR = 3.12; 95% CI: 2.06–4.72; $p < 0.01$), and in younger age groups, the risk exhibited a 3.28-fold decrease (adjusted OR = 3.28; 95% CI: 2.66–4.04; $p < 0.01$).

Conclusion: The present results suggest that receiving at least one dose of COVID-19 vaccine had a significant relationship with decreased COVID-19 severity and mortality in vaccinated patients compared to unvaccinated patients.

Fatemeh Hasani and Zahra Norouzi contributed equally to this study.

1 | Introduction

Coronavirus disease 2019 (COVID-19), which originated from Wuhan, China, started to spread around the world since November 2019. On March 11, 2020, the World Health Organization (WHO) declared it as pandemics around the world. From December, 2019 until November 8, 2021, more than 250 million cases of COVID-19 were reported. Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is the virus responsible for COVID-19. According to WHO reports, this virus is responsible for the death of over five million people in more than 200 countries [1].

The spike glycoprotein on the surface of virion binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is the main target for the virus and is located on the surface of host cells. ACE2 receptors help the virus enter its RNA to the host cell cytoplasm and cause infection [2]. As of May 31, 2021, the WHO reported four variants of concern: Alpha, Beta, Gamma, and Delta. These variants, particularly those with mutations in the receptor binding domain of the spike gene (S gene), have been associated with increased transmission and severity of the disease. The prevalence and spread of the Delta variant of coronavirus has surpassed other variants in most countries. This variant's elevated transmission ability can substantially reduce vaccine effectiveness, increasing the likelihood of breakthrough infections [3–9].

The spread of the Delta variant of coronavirus started in June 2021 and accounted for the fifth peak of COVID-19 in Iran in July 2021 [10]. Golestan province was one of the hardest-hit regions with approximately 57% of COVID-19 exposure [11]. Although the number of hospitalized (21.5%) and positive (32.4%) SARS-CoV-2 northern Iranian patients during the fifth wave was more than twice other waves, the mortality rates were less than one-third of all waves before the delta spread, suggesting the role of vaccination in lowering COVID-19 mortality [12].

According to reports from other countries, vaccination protects against severe diseases caused by COVID-19, including the Delta variant. Studies have also shown that vaccination provides strong protection against SARS-CoV-2 infection, COVID-19-related hospitalization, and mortality. Moreover, it has been reported that both full and partial vaccination can be greatly effective against the severe outcomes of COVID-19-related hospitalization and mortality; one study was conducted in England assessing the roles of Pfizer-BioNTech and Oxford-AstraZeneca vaccines, and the other study was based on U.S. jurisdictions who received mRNA vaccines (a Pfizer-BioNTech or Moderna), or Janssen (Johnson & Johnson) vaccine [13, 14].

Iran, with a population of 83 million people, is one of the top 10 countries in terms of COVID-19-related mortality. As of November 8, 2021, Iran reported more than six million confirmed cases of COVID-19 and over 127,000 deaths [14]. Vaccination was initiated in January 2021. The first vaccinated groups included the healthcare personnel and frontline workers. Also, mass vaccination started in May 2021. The present study aimed to evaluate the mortality and severity of the 2,962 confirmed cases of Delta variant in vaccinated patients versus unvaccinated patients, admitted to Sayyad Shirazi Hospital in Gorgan, Iran, during the fifth peak of COVID-19, caused by the Delta variant between June 22, 2021, and September 22, 2021.

2 | Materials and Methods

2.1 | Study Design

This study was conducted in a tertiary hospital of Golestan province. Golestan with a population of 1.8 million (2016) is located in the north-west of Iran. People of this province are from different races like Mazandarani, Turkmen, Baluch, Persian, Kazakh, Kurd, and Azeri [13]. The importance of this wide variety of races in our province is that the results could be applied to Iranian population. This retrospective cohort study was designed based on the medical care monitoring center (MCMC) database of Sayyad Shirazi Hospital in Golestan Province, Iran.

2.2 | Participants

The inclusion criteria for patient selection encompassed adults aged 18 and above, with confirmation through polymerase chain reaction (PCR) testing on respiratory samples. Additionally, individuals with negative PCR results but presenting clinical manifestations consistent with COVID-19 and corresponding findings on chest CT scans were also considered. Between June 22, 2021, and September 22, 2021, a total of 2964 COVID-19 cases were admitted to this hospital during the Delta variant spread. The study considered all COVID-19 admitted patients within this timeframe. All the patients were examined for a history of confirmed COVID-19 infection, based on standard laboratory protocols.

2.3 | Exposure and Outcomes

The following patient data were extracted from electronic medical records and MCMC database of Sayyad Shirazi Hospital for this study: demographic characteristics, signs and symptoms, ICU admission, need for aggressive oxygen therapy, including intubation, mortality, and vaccination status (partial or full). Individuals receiving one or two doses of vaccine were considered to be vaccinated. Patients who completed two doses of vaccination at least 2 weeks before symptoms, were considered fully vaccinated, while those who received one dose in 14 days to onset of symptoms or the second dose of vaccine within the 2 weeks of symptoms were considered to be partially vaccinated [15]. Available vaccines during study period in Golestan province were AstraZeneca (adenovector-based), Sinopharm (inactivated), Sputnik (adenovector-based), Co-Iran Barakat (inactivated), and Co-pars (protein-based). In Iran, vaccination was started in January 2021. Initially, the healthcare personnel and frontline workers were inoculated by Sputnik. Mass vaccination started in May 2021. By the end of January 2022, five vaccines produced in Iran, COVIran Barekat, SpikoGen, PastoCovac, FAKHRAVAC, and Razi Cov Pars received emergency license [11, 16, 17]. Up to May 15, 2023, 175.46 doses per 100 people of these vaccines were administered [18], thus according to very low number of fully vaccinated

patients, we pooled different vaccination status and compared vaccinated with unvaccinated patients.

We defined Severe COVID-19 according to the 2019 clinical practice guideline of the Infectious Diseases Society of America [19]. Patients who had either one major, or above three minor criteria were considered severe COVID-19 patients. Major criteria were Septic shock with need for vasopressors, and requiring mechanical ventilation. Minor criteria were as follows: hypotension in need of aggressive fluid resuscitation, temperature under 36°C, respiratory rates more than 30 breaths/min, altered mental status, and multilobar infiltrates, as well as laboratory findings such as platelet count lower than 100,000/μL, white blood cell count < 4000 cells/μL, blood urea nitrogen concentration 20 mg/dL or above.

The primary outcome of the study was death. In the next place, disease severity as well as morbidity and mortality associated factors.

2.4 | Statistical Analysis

Descriptive statistics were applied to summarize the numerical variables as mean, standard deviation (SD). Categorical variables were presented as frequency and proportions. Fisher's exact test or chi square was used to evaluate the association between basic characteristics of subjects between groups (vaccinated vs. unvaccinated). The mean difference was assessed using t-test, while the difference between proportions was compared with z-test. A multivariate logistic regression analysis was performed to assess the association of COVID-19 severity as well as mortality with vaccination status and other covariates such as age and gender. Crude and adjusted odds ratios (OR) and their 95% confidence intervals (CIs) were also calculated by comparing the odds of the severe COVID-19 or death among vaccinated subjects with those among unvaccinated patients. For sensitivity assessment, a similar analysis was carried out by restricting the data to only PCR-positive cases. A p value less than 0.05 was considered statistically significant. Statistical analyses were carried out using SPSS version 16.

3 | Ethics Approval

The local ethics committee at Golestan University of Medical Science approved this retrospective study (IR. GOUMS. REC.1400.307) according to the 1964 Helsinki declaration and its later amendments. The patient data was appropriately anonymized and maintained with confidentiality. Informed consent was obtained via phone calls from all individual participants included in the study. In case of patients' death, we called a family member, parents, siblings, or spouses according the available documentary.

4 | Results

A total of 2,962 confirmed cases of COVID-19, with a mean (SD) age of 51.33 (16.22) years, who were admitted to Sayyad Shirazi Hospital in Shiraz, Iran, were included in this study. Among all participants, 1597 (53.9%) were female. The demographic characteristics of the patients are presented in Table 1. The median length of hospital stay was 6 (3–14) among all of patients, 4 (3–8) among vaccinated patients and 5 (4–14) among non-vaccinated subjects. Among all patients, 524 (17.8%) had severe COVID-19. Overall, 5.2% (27/524) of the patients were vaccinated, while 94.8% (497/524) were unvaccinated. The frequency of symptoms of COVID-19 observed in patients are summarized in Table 2. The most common was respiratory symptoms consisting in 70.1% of patients, moreover fever, myalgia, and gastrointestinal symptoms stood in the next places respectively.

Severe COVID-19 was significantly related to vaccination (adjusted OR = 3.12; 95% CI: 2.06–4.72; $p < 0.01$) and age (adjusted OR = 3.28; 95% CI: 2.66–4.04; $p < 0.01$).

A total of 269 (9.0%) patients died during the study, of which all of them were patients admitted with severe disease. Out of the patients who died, only 4.1% were vaccinated, while 95.9% were unvaccinated. Based on the results, being vaccinated (adjusted OR = 4.14; 95% CI: 2.22–7.69; $p < 0.01$) and a younger age group (adjusted OR = 5.58; 95% CI: 4.25–8.14; $p < 0.01$) were significantly associated with a lower mortality (Table 3).

The results of sensitivity analysis on 1737 cases suggested that severe COVID-19 had a significant relationship with not receiving vaccines (adjusted OR = 3.04, 95% CI: 1.64–5.65,

TABLE 1 | Demographic characteristics of confirmed COVID-19 patients admitted to Sayyad Shirazi Hospital.

Variable		Number	Percentage
Gender	Male	1365	46.1
	Female	1597	53.9
Age (years)	≤ 50	1466	49.5
	> 50	1496	50.5
COVID-19 diagnostic method	PCR	1737	58.6
	Clinical/CT	1225	41.4
Vaccination status	Vaccinated	281	9.5
	Unvaccinated	2681	90.5
Health staff	Yes	30	1.0
	No	2932	99.0

TABLE 2 | Symptoms observed in COVID-19 patients admitted to Sayyad Shirazi Hospital, Gorgan, between June 22 and September 22, 2021.

Sign and symptoms	Number	Percentage
Fever	1365	46.1
Respiratory symptoms	2077	70.1
Myalgia	807	27.2
Gastrointestinal symptoms	718	24.2
Neurological symptoms	555	18.7

$p < 0.01$) and ages above 50-years-old (adjusted OR = 3.71, 95% CI: 2.83–4.86, $p < 0.01$). Overall, 169 cases died in hospital, including 162 (95.8%) unvaccinated cases and 139 (82.2%) cases older than 50 years. Vaccination (adjusted OR = 2.74; 95% CI: 1.25–6.04; $p < 0.01$) and age > 50 (adjusted OR = 6.01, 95% CI: 3.99–9.05, $p < 0.01$) were significantly related to mortality in PCR-positive cases (Table 4).

TABLE 3 | Association between vaccination status and severity or mortality of COVID-19 in patients (both PCR positive and CT scan positive) admitted to Sayyad Shirazi Hospital, Gorgan, between June 22 and September 22, 2021. Crude and adjusted odds ratios (OR) and their 95% confidence intervals (CIs) were also calculated by comparing the odds of the severe COVID-19 or death among vaccinated subjects with those among unvaccinated patients. A p value less than 0.05 was considered statistically significant. Ref stands for reference category which is a baseline used to compare the odds.

		Severe COVID-19							Mortality						
		Crude				Adjusted			Crude				Adjusted		
Variable		*N* (%)	OR	95% CI	*p* value	OR	95% CI	*p* value	*N* (%)	OR	95% CI	*p* value	OR	95% CI	*p* value
Gender	Male	257/1356 (18.8)	1.15	0.96–1.39	0.13	1.15	0.95–1.39	0.16	132/1365 (9.7)	1.14	0.89–1.47	0.30	—	—	—
	Female	267/1597 (16.7)	Ref.	Ref.	—	Ref.	Ref.	—	137/1597 (8.6)	Ref.	Ref.	—	—	—	—
Age (years)	≤ 50	149/1466 (10.1)	Ref.	Ref.	—	Ref.	Ref.	—	47/1466 (3.2)	Ref.	Ref.	—	Ref.	Ref.	—
	> 50	375/1496 (25.0)	2.96	2.41–3.63	$p < 0.01$	3.28	2.66–4.04	$p < 0.01$	222/1496 (14.8)	5.26	3.87–7.27	$p < 0.01$	5.88	4.25–8.14	$p < 0.01$
Vaccine	Yes	27/281 (9.6)	Ref.	Ref.	—	Ref.	Ref.	—	11/281 (3.9)	Ref.	Ref.	—	Ref.	Ref.	—
	No	497/2681 (18.5)	2.14	1.423–3.221	$p < 0.01$	3.12	2.06–4.72	$p < 0.01$	258/2681 (9.6)	2.61	1.41–4.84	0.002	4.14	2.22–7.69	$p < 0.01$

5 | Discussion

Iran has experienced five waves of the COVID-19 pandemic until the end of summer 2021, with the death of over 127,000 people and major economic, medical, and social consequences. The number of COVID-19 patients began to rise in June, reaching the peak during the fifth wave caused by the Delta variant in July 2021. Since June 2021, the majority of new COVID-19 cases in Iran have been caused by the Delta variant [4]. The present results suggest that COVID-19 severity is 3.12 times higher in unvaccinated patients, and also, COVID-19 mortality is 4.14 times higher in unvaccinated patients, although at the time of study most of the patients were not fully vaccinated. We also found strong evidence of age dependence in the extent of risk reduction.

Based on the current findings, vaccination demonstrated a significant positive association with a lower risk of severe COVID-19 and a decrease in mortality rates. In a study published in 2021, Noa Dagan et al. estimated that the effectiveness of COVID-19 vaccination (BNT162b2 mRNA) against severe disease and death in Isreal was 80% and 84%, respectively. They enrolled 596,618 participants in each vaccinated and unvaccinated groups [20]. Abhilash et al. in an Indian cohort study contained 4183 patients, estimated the mortality rate of COVID-19 to be 0.2% (95% CI: 0.2%–0.7%) and 12.9% (95% CI: 11.8%–14.1%) in fully Covishield, or Covaxin vaccinated versus unvaccinated patients, respectively. They also indicated that at least one dose of vaccine was significantly associated with a lower disease severity (RR: 0.40; 95% CI: 0.35–0.47), need for respiratory support (RR: 0.33; 95% CI: 0.27–0.40), ICU admission (RR: 0.18; 95% CI: 0.12–0.27), and mortality (RR: 0.18; 95% CI: 0.11–0.29). Their findings showed that full vaccination reduced the need for oxygen therapy, noninvasive ventilation, hospitalization, ICU admission, and mortality [21]. The rate of severe COVID-19 was 18.5% in unvaccinated patients in the current study. In a systematic review of 12 studies, consisting of 2794 COVID-19 patients, 21.33% had a severe disease [22]. In another meta-analysis which also included 12 studies on 2445 patients, admitted to the hospitals of China, 479 (19.9%) cases had a severe illness or were admitted to the ICU [23]. In our study, 21.2% of patients in the unvaccinated group had a critical disease related to COVID-19, which is consistent with the findings of other systematic reviews (19.9% and 21.33%), respectively [22, 23].

Other studies have also indicated the effectiveness of COVID-19 vaccination. In a large retrospective cohort study on 15,244 patients during the Delta variant spread in North India, two doses of Inactivated Whole Virion Vaccine BBV152 caused greater protection against reinfection [24]. Moreover, in a large integrated health system study conducted in Southern

TABLE 4 | Association between vaccination status and severity or mortality of COVID-19 in PCR-positive patients admitted to Sayyad Shirazi Hospital, Gorgan, from June 22 to September 22, 2021. Crude and adjusted odds ratios (OR) and their 95% confidence intervals (CIs) were also calculated by comparing the odds of the severe COVID-19 or death among vaccinated subjects with those among unvaccinated patients. A p value less than 0.05 was considered statistically significant. Ref stands for reference category which is a baseline used to compare the odds.

		Severe COVID-19							Mortality						
			Crude			Adjusted				Crude			Adjusted		
Variable		*N* (%)	OR	95% CI	p value	OR	95% CI	p value	*N* (%)	OR	95% CI	p value	OR	95% CI	p value
Gender	Male	157/795 (19.7)	1.18	0.922–1.499	0.19	1.16	0.90–1.49	0.25	85/795 (10.6)	1.22	0.89–1.68	0.21	—	—	—
	Female	163/942 (17.3)	Ref.	Ref.	—	Ref.	Ref.	—	84/942 (8.9)	Ref.	Ref.	—	—	—	—
Age	≤ 50	88/891 (9.8)	Ref.	Ref.	—	Ref.	Ref.	—	30/891 (3.3)	Ref.	Ref.	—	Ref.	Ref.	—
	> 50	232/846 (27.4)	3.45	2.64–4.50	$p < 0.01$	3.71	2.83–4.86	$p < 0.01$	139/846 (16.4)	5.64	3.75–8.48	$p < 0.01$	6.01	3.99–9.05	$p < 0.01$
Vaccine	Yes	12/116 (10.3)	Ref.	Ref.	—	Ref.	Ref.	—	7/116 (6.3)	Ref.	Ref.	—	Ref.	Ref.	—
	No	308/1621 (19.0)	2.03	1.10–3.74	0.02	3.04	1.64–5.65	$p < 0.01$	162/1621 (9.9)	1.73	0.79–3.78	0.17	2.74	1.25–6.04	0.01

California ($N = 3,436,957$), Tartof et al. reported that fully vaccinated individuals had an adjusted mRNA BNT162b2 COVID-19 vaccine effectiveness of 73% (95% CI: 72–74) against SARS-CoV-2 infection and 90% (95% CI: 89–92) against COVID-19-related hospitalization in United States [25]. Besides, Ali Pormohammad et al. in a meta-analysis of 15 studies concluded that vaccination can prevent COVID-19 infection, and reduce the severity of disease and hospitalization against the Delta variant [26]. Noteworthy, vaccination did not also increase all-cause mortality, non-COVID-19 vaccine, or cardiac-related death rates among healthy receivers. A retrospective cohort study by Xu et al. on patients receiving all three vaccines in United States, reported that even crude non-COVID-19 mortality was lower among vaccinated subjects [27]. A recent self-controlled case-series also revealed that there was no increased risk of non-COVID-19 mortality among Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Janssen (Ad26. COV2.S) recipients in United States [28].

Eric J. Haas et al. used the national surveillance data to show that in all age groups, by increasing vaccine coverage, the incidence of negative SARS-CoV-2 outcomes declined. Their findings indicated that vaccine effectiveness was 95.3% against SARS-CoV-2 infection (95% CI: 94.9 –95.79), 97.2% against COVID-19-related hospitalization (95% CI: 96.8–97.5), 97.5% against severe or critical COVID-19-related hospitalization (95% CI: 97.1 to 97.8), and 96.7% against COVID-19-related death (95% CI: 96.0–97.3). The findings of this study, similar to the current study, showed the high effectiveness of mRNA BNT162b2 vaccination in reducing death and preventing the increased severity of this disease in Israelian population [29]. Another study by Jamie Lopez Bernal et al. with a population of 174,731, indicated that Pfizer-BioNTech and Oxford-AstraZeneca vaccines could significantly reduce COVID-19 symptoms in older adults and protect against a severe disease. The effectiveness of vaccination was 43% in reducing the risk of emergency hospital admission (33%–52%) and 51% (37%–62%) in reducing the risk of mortality in vaccinated patients compared to unvaccinated ones in England [13].

Our study confirmed that older age is a risk factor for severe COVID-19 (adjusted OR: 3.28; 95% CI: 2.66–4.04) and COVID-19 mortality (adjusted OR: 5.88; 95% CI: 4.28–8.14). In line with the current findings, Xiaochen Li et al. reported that age over 65 years was significantly associated with severe COVID-19 (adjusted OR: 2.2; 95% CI: 1.5–3.5) [30]. Moreover, in a study by J. Zhang et al., it was found that age above 60 years was associated with a lack of improvement in hospitalization, poor condition, and poor outcomes. Overall, older COVID-19 patients were significantly more likely to die in hospital [31]. It seems that age-related changes in the adaptive immune response can lead to an increased risk of infection in elderly patients, as defects in both cell-mediated and humoral immunity progressively increase with age, resulting in a marked increase in the incidence of severe infection [32, 33].

This study highlights the importance of vaccination during infectious pandemics, disregarding the brand and mechanism of action, in lowering mortality rates. According to different population-based characteristics of COVID-19, immunity caused by vaccinations, and varied vaccine types, this study

focus on Iranian population in Golestan Hospital with diverse races. This study has considerable strengths. First, we included a large population of COVID-19 patient. Second, we focused on Delta wave in Iran, and evaluated only the effect of vaccination on COVID-19 mortality disregarding mechanism of action of vaccines or doses. Our study also had considerable limitations. Unfortunately, reliable comorbidity data was not available for this study. This study combines individuals who are partially and fully vaccinated into one group due to the low ratio of fully vaccinated individuals. However, the immunity provided by one dose versus two doses can significantly differ, and combining these two groups can misrepresent the actual impacts. The definitions of COVID-19 related severity can be based on different guidelines in studies, so it should be considered when interpreting the results. Another limitation of the study is the inclusion of patients with negative PCR results but positive CT findings as COVID-19 cases. This approach may introduce bias if the CT findings are not confirmed with COVID-19-specific symptoms or repeat PCR testing.

6 | Conclusion

According to findings elucidated in this study, which underscore a substantial positive association between vaccination and diminished severity of COVID-19 coupled with a noteworthy reduction in mortality rates, it is imperative to direct attention towards future research endeavors to delve into the longitudinal effects of vaccination, the potential efficacy of booster doses, and the intricate dynamics of emerging variants, thereby contributing valuable insights to the ongoing discourse on public health strategies.

Author Contributions

Fatemeh Hasani: design and conceptualization, data collection, analysis, initial drafting. **Zahra Norouzi:** design and conceptualization, software, validation, initial drafting. **Kimia Jazi:** design and conceptualization, data collection, Critical revise of the first draft, Project administration. **Gholamreza Roshandel:** design and conceptualization, Investigation, data collection, initial drafting. **Alireza Norouzi:** design and conceptualization, supervision, visualization, critical revise of the first draft. All authors have read and approved the final version of the manuscript. All authors acknowledge their responsibility for the entirety of the work, committing to promptly and appropriately investigate and resolve any concerns regarding accuracy or integrity. Alireza Norouzi had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Transparency Statement

The lead author Alireza Norouzi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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