Original Article

COVID-19 Vaccines Side-Effects and Reaction Among Vaccinated Population in Saudi Arabia

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Abstract

Several COVID-19 vaccines have been developed and authorized for emergency use by various regulatory agencies worldwide. Objective: to compare the adverse effects and safety of confirmed COVID-19 vaccines in Saudi Arabia and provide a centralized database of suspected adverse reactions and safety profiles to these vaccines. In this cross-sectional study, the study was conducted among the 633 vaccinated participants living in Saudi Arabia through an online questionnaire. Their age group was between 15-85 years old. The study indicated that 55% of the participants were infected with COVID-19, and 33% were infected before vaccination. 10% of our study participants had two or more related comorbidities, commonly hypertension, respiratory problems, and diabetes mellitus. The most frequent side effects of these vaccines are fatigue, headaches, fever, myalgia, arthralgia, pain, tenderness, and swelling at the injection site, especially after the first dose. Commonly systemic side effects presented in young female participants, 15-30 years old. This study postulates a database about the possibility of developing COVID-19 vaccine adverse effects based on age, gender, comorbidities, and vaccine type. More research must be done to understand more clearly the association between developing adverse effects and risk factors.

Keywords: SARS-CoV-2, COVID-19 vaccines, Pfizer-BioNTech, Moderna, Oxford/AstraZeneca

Introduction

It is remarkable how quickly several vaccines were developed and tested against severe acute respiratory corona Virus 2 (SARS-CoV-2) that caused the 2019 coronavirus disease (COVID-19) [1]. Many vaccines produced have outperformed predictions, and there are high expectations that the epidemic will end soon. Today, billions of vaccine doses have been provided Worldwide [2]. In December 2020, the first COVID-19 vaccinations were approved for emergency use in the United States [3, 4]. Vaccine hesitancy (VH) is delaying or not getting vaccines even though vaccine services are available [5]. This growing public health problem is made worse by false beliefs about the efficacy and safety of vaccines [6]. Most of what is known about COVID-19 vaccine safety comes from manufacturer-funded studies conducted following guidelines established by the appropriate drug regulatory authorities and overseen by independent experts. Adverse events documented in controlled trials with COVID-19 vaccines included injection site events (e.g., discomfort, erythema, edema) and systemic effects (e.g., tiredness, headache, muscular or joint aching), with rarely significant unwanted reactions [7-10]. Researchers estimated that fifty to ninety percent of subjects experienced unfavorable reactions, though most were mild [8-10]. While data on adverse reactions recorded by government-sponsored monitoring platforms have started to surface [11-13], there is little actual, patient-reported evidence on adverse consequences following the COVID-19 vaccination and who is more likely to have them.

Some have developed several potential COVID-19 vaccines for the world's largest pharmaceutical corporations. The Pfizer/BioNTech Comirnaty vaccine was the first COVID-19 vaccine to be added to the World Health Organization (WHO's) Emergency Use List (EUL) on December 31, 2020. The AstraZeneca AZD1222 and SII Covishield vaccines from AstraZeneca/Oxford were licensed for EUL on February 16, 2021; the Johnson & Johnson Janssen Ad26.COV 2.S vaccine was approved on March 12, 2021, and the Moderna COVID-19 vaccine (mRNA 1273) was approved on April 30, 2021. The most well-known RNA vaccine is the Pfizer-BioNTech COVID-19 vaccine. It consists of a fat nanosphere containing a nucleoside-modified mRNA expressing the SARS-CoV-2 full-length spike (S) protein [14-16]. On December 10, 2020,

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the Kingdom of Saudi Arabia's (KSA) Saudi Food and Drug Authority (SFDA) approved this vaccine for emergency use [17]. The main problem with this vaccine is that it requires very low-temperature storage and can only be stored at room temperature for two hours. Also, it is incompatible with other vaccines. The only contraindication is a history of severe hypersensitivity responses to any vaccine ingredient [18]. Moderna developed the second RNA vaccine, mRNA-1273, a fat nanosphere containing mRNA. It achieved 94% efficacy in a Phase III clinical study and is recommended for adults over 18. Similar to the Pfizer-BioNTech BNT162b2 COVID-19 vaccine, it must be frozen but at higher temperatures and can be stored at two °C to eight °C for a maximum of thirty days. It has the same side effects as BNT162b2, with pain at the injection site being the most common. It should not be given to pregnant or lactating women or children. Also, it cannot be substituted for other vaccinations, and the possible primary barrier is a history of severe allergic reactions to any of the vaccine's components [19]. Several viral vector vaccines have been made, including the chimpanzee adenovirus-vectored ChAdOx1 nCov-19 vaccine made by Oxford/AstraZeneca. Its Phase III study got off to a rough start on September 8, 2020, when worries about transverse myelitis came up. The study was put on hold for seven days. Despite these differences, both schedules reported a 70% overall efficacy with a generally adequate safety requirement [8, 20]. This study aimed to assess COVID-19 vaccine adverse effects and reactions among the vaccinated population in Saudi Arabia and to provide a database of the differences between these confirmed vaccines in Saudi Arabia and their safety.

Materials and Methods

On 10th August 2022, a cross-sectional survey was conducted to evaluate the adverse effects and reactions of the different COVID-19 vaccination types in Saudi Arabian citizens. Before collecting data, the consent form was obtained from all participants electronically, and only those who agreed could complete the survey online. The study was approved by the Scientific Research Ethics Committee at Taif University (Research number/44-014).

This study involved 633 participants who consented and completed the online questionnaire with an age range of 15–85 years. All participants were residing in Saudi Arabia and had taken the first dose or the entire course of the vaccine (two doses) or booster in addition to the two doses at least 30 days before the trial. The questionnaire asked about the respondents' age, gender, weight, and whether or not they smoked. It also asked about their comorbidities (cardiovascular, respiratory, renal, hepatic, immunological, and endocrine diseases), the type and number of vaccines they got, their symptoms after vaccination, and how long they lasted. Thus, the effectiveness of these vaccines was measured by assessing the number of infected with COVID-19 before and after vaccination. The occurrence of these adverse events was evaluated and studied to determine which symptoms are the most common and which vaccine type may be associated with them.

Statistical analysis: In this study, Prism 8 for OS X (version 8.4.3 of GraphicPad Software, LLC) was used for statistical analysis. To compare continuous variables, chi-square, t-test, and one-way ANOVA were used. P values < 0.05 were considered statistically significant.

Results and Discussion

The reactions and side effects of the COVID-19 vaccine in Saudi Arabia were evaluated. There were 633 participants interested in responding to the questionnaire. Most of the study's 397 (62.7%) females and 236 (37.3%) males were between the ages of 15 to 85 years old, with a mean age of 27.6±12.29 years old. A total of 566 (89.4%) of the participants were nonsmokers, and 547 (86.4%) were either university graduates or current students at the university. 443 (70%) of the subjects were unemployed. Most of the participants had a normal body mass index (BMI) of 48.7% (n=308), followed by 23.3% of the participants who were overweight (n=147), then 13.7% of them were obese (n=87) **(Table 1)**.

Table 1. Demographic characteristics of research subjects.

Variable	Characteristic	Total (n)	Total (%)
Gender	Female	397	62.7
	Male	236	37.3
Age	15-30	438	69.2
	31-45	125	19.7
	46-60	62	9.8
	61-75	6	1
	> 76	2	0.3
Smoking	No	566	89.4
	Yes	67	10.6
Education level	Primary	4	0.6
	Secondary	82	13
	University	547	86.4
Employment	Unemployed	443	70
	Employed	190	30
BMI	Underweight	84	13.3
	Normal	308	48.7
	Overweight	147	23.3
	Obese	87	13.7
	Extremely obese	7	1.1

Two hundred ninety-two respondents (46.3%) reported having been infected with COVID-19 at some point **(Figure 1a)**: 225 people (77.1%) had been exposed to the virus only once, 58 participants (19.9%) had been exposed to the virus twice, and 9 participants (3%) had been exposed three times **(Figure 1b)**. Over half of the respondents were infected with COVID-19 (n=352, 55%). Approximately 33% of infected participants (n=117) had the infection before receiving the first dose of vaccines, followed by approximately 30% of participants in this survey (n=104) who were infected with

COVID-19 after the second dose. Fifty participants (about 14 %) became infected after the first dose, 78 participants (around 22 %) became infected after the third dose (1st booster dose), and only 3 participants became infected after the fourth dose (2nd booster dose) **(Figure 1c)**.

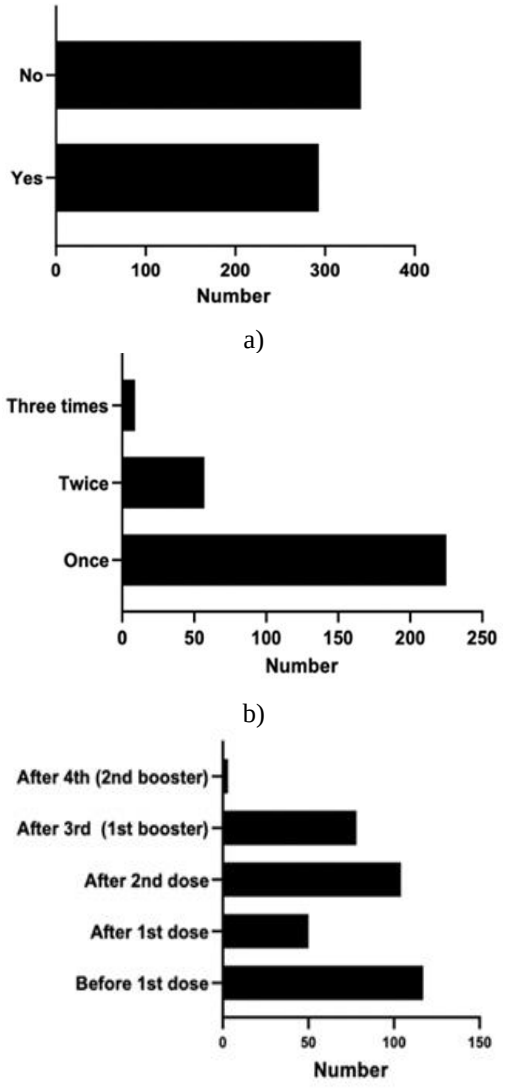


Figure 1. COVID-19 infection history and frequency in the individuals included in the study. a) the number of individuals previously infected with SARS-CoV-2. b) The number of COVID-19 infections. c) Infected with SARS-CoV-2 either before or after vaccination.

Participants in our study were questioned about the type of vaccine they received: 504 (around 80%) received the first dose of Pfizer, 117 (18%) received AstraZeneca, and 12 (2%) received Moderna. In the second dose, the most prominent COVID-19 vaccine type was Pfizer, then Moderna, and AstraZeneca, with total vaccinated participants of 501, 72, and 60, respectively. Consistently, the first booster dose was Pfizer's (n=451), Moderna's (n=104), and AstraZeneca's (n=34). Thus, the total number of participants who had the first booster dose was 589 (93%). While the second booster dose included 284 (45%) participants; 240 Pfizer, 28 Moderna, and 16 AstraZeneca **(Figure 2)**. The number of participants, who had boosters, was lower than in the first and the second doses because not all of the participants agreed to have the boosters, while the first and the second doses were compulsory in Saudi Arabia.

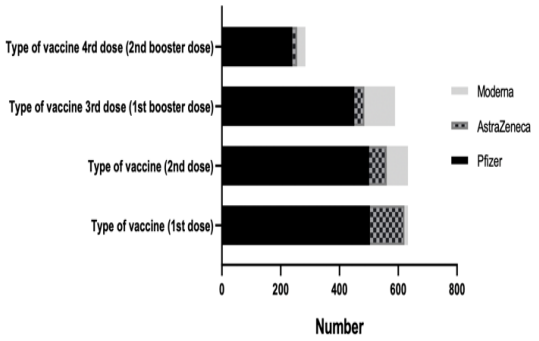
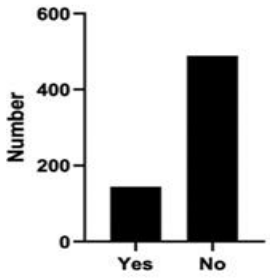
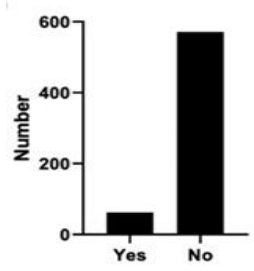
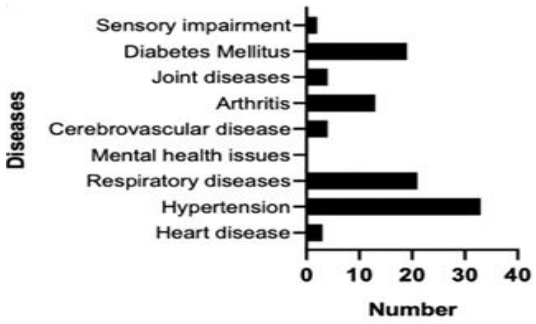


Figure 2. Types of COVID-19 vaccines in Saudi Arabia.

In the current survey, about 77% of the participants (n=489) did not have any allergy; however, 23% had an allergy (n=144) **(Figure 3a)**. In addition, 570 respondents (90%) had no related comorbid conditions compared to 63 respondents (10%) with comorbidities **(Figure 3b)**. The participants who took part in our study were most likely to have hypertension approximately 34%, respiratory problems (22%), diabetes mellitus (20%), arthritis (13%), and other diseases (11%) **(Figure 3c)**. **Table 2** shows no statistically significant difference between individuals with COVID-19 infection before vaccination and without COVID-19 infection.







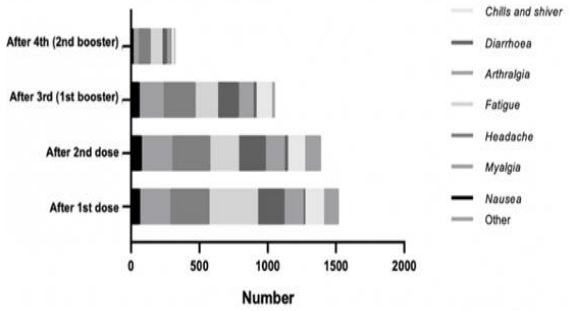
c)

Figure 3. Allergy and Comorbidity before COVID-19 vaccination. a) The number of individuals with allergies, b) The number of individuals with comorbidities. c) Comorbid diseases.

Table 2. COVID-19 infection and comorbid disease.

Comorbid diseases	COVID-19 Infection		t-test	*P* value
	Yes	No		
Hypertension	22	11	1.364	0.3057
Diabetes Mellitus	9	10	0.3162	0.7676
Respiratory diseases	11	10	0.3111	0.7663
Arthritis	5	8	0.6000	0.6094
Cerebrovascular disease	2	0	1.000	0.4226
Joint disease	2	2	0.000	>0.9999
Heart Disease	1	2	0.4472	0.6985
Sensory impairment	1	1	0.000	>0.9999

In our survey, approximately 74% of the participants (n=466) had side effects after COVID-19 vaccinations. Fatigue, headaches, myalgia, fever, chills and shiver, and arthralgia were the most common systemic side effects of COVID-19 after the first and second doses, as well as the first booster doses **(Figure 4a)**. Pain, tenderness, and swelling at the injection site were the most common local side effects of the first, second doses, and booster doses for all study participants **(Figure 4b)**. It has been demonstrated that the most severe side effects were after the first dose (43%), followed by the second dose (34%), using mainly Pfizer and /or AstraZeneca vaccines. The side effects were more common in young people between 15 and 30 years old (n=323 out of 438) compared to other age groups; 31-45 and 46-85 years old (n=92 out of 125, and n=51 out of 70 receptively) **(Figure 5a)**. Women experienced more systemic side effects (n=303 out of 397) than men **(Figure 5b)**.



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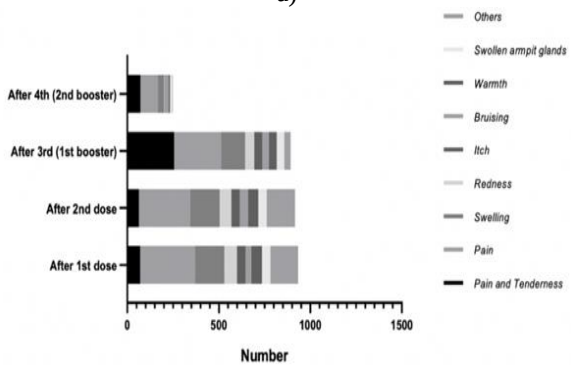
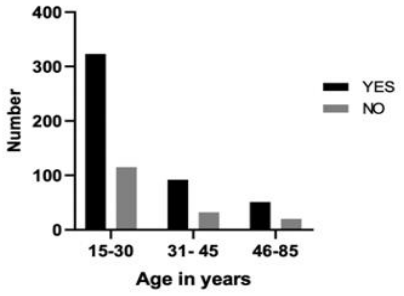


b)

Figure 4. COVID-19 vaccine side effects. a) Systemic side effects. b) Local side effects.



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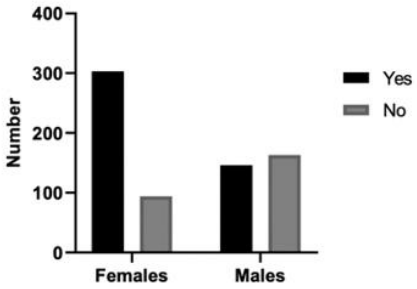

b)

Figure 5. Systemic side effects of the COVID-19 vaccine depend on; a) Age and b) Gender of participants.

The COVID-19 outbreak quickly spread worldwide, causing a major health crisis [21]. Early in 2020, when the COVID-

19 pandemic began, most countries took precautionary measures to prevent the spread of SARS-CoV-2, expecting that rapidly manufactured, reliable, and effective vaccines would be available [22]. The production of COVID-19 vaccines evolved quickly when regulatory and medical judgments had to focus on benefit and risk estimations, defining priorities, and potential achievements [23]. In July 2021, at least one government agency approved using 18 vaccines for emergency use; 185 COVID-19 vaccine candidates were in pre-clinical testing, and 105 were in clinical development [24]. Saudi Arabia has begun an early vaccination campaign as part of its early and impressive efforts to halt the spread of SARS-CoV-2. This study aimed to evaluate the side effects frequency and reactions of COVID-19-approved vaccines in Saudi Arabia. Our study indicated that approximately 55% of our participants were infected with COVID-19 once, twice, or three times. 33% out of this percentage had been infected with COVID-19 before vaccination. However, 14% of participants after receiving the first dose of the vaccine, followed by 33% after the second dose, 22% after the first booster, and 1% after the second booster. 10% of our study participants had two or more health issues simultaneously, commonly high blood pressure, respiratory problems, and diabetes mellitus. These findings could interpret the response of the immune system when infected with COVID-19, which stimulates cellular and humoral immunity [15, 25]. While it is possible to become infected with COVID-19 more than once, the likelihood and frequency of reinfection appear relatively low. Several factors may influence an individual's susceptibility to reinfection with COVID-19, including the severity of the initial infection, the individual's immune response, and the emergence of new virus variants. Research has shown that individuals who recover from COVID-19 develop a strong immune response, including the production of antibodies, which may provide some level of protection against reinfection. However, the duration and strength of the immune response may vary from person to person, and it is not yet clear how long the protection from reinfection lasts exactly. Therefore, vaccination against COVID-19 has been shown to produce a strong immune response, which can protect against the virus and its variants. The vaccines are highly effective in preventing hospitalization, severe illness, and death from COVID-19 [15]. Several studies validated that the antibody concentration is higher in individuals with a history of COVID-19 infection [26-28].

In addition, 23% of the participants suffered from allergies with allergic reactions (e.g. rash, skin burning, red welts on face and lips). These individuals may be at high risk of developing severe illness from COVID-19. While having allergies is not a direct risk factor for COVID-19, it can weaken the immune system and increase the risk of developing severe illnesses to eliminate the virus [29].

In our survey, approximately 74% of the participants (n=466) experienced adverse effects related to COVID-19 vaccinations. Fatigue, headaches, myalgia, chills and shivers, and arthralgia were the most common systemic side effects of COVID-19 after the first and second doses and the first booster doses **(Figure 4a)**. At the same time, pain, tenderness, and swelling at the injection site were the most common local side effects of the first, second, and booster doses for all study participants **(Figure 4b)**. This is because of the mediation of the innate immune system. When macrophages or neutrophils identify vaccine proteins, they produce cytokines that activate immunological reactions such as fever, shivers, nausea, and muscular aches. Most adverse effects are mild and last between 24 and 48 hours. The participant's age, gender, and dosage influence the variability [8]. These data were consistent with results demonstrated by Alhazmi *et al*. [30, 31] reported that 60–80% of side effects were associated with both Pfizer and AstraZeneca vaccines. Furthermore, a recent study documented similar side effects for participants who received the same vaccines [32]. The Pfizer-BioNTech vaccine was given to most of our participants (approximately 75-80%) in the first, the second doses, and boosters. Generally, most of our young participants, 15-30 years old, were more likely to have systemic side effects because the immune systems are stronger and more efficient in a younger population, but this difference was not statistically significant. Alhazmi and his colleagues revealed similar findings about systemic adverse effects [30, 33]. The fact that AstraZeneca's vaccine was administered to the majority of the young people who experienced systemic reactions may explain this. In some studies, younger people are more likely than older people to report adverse effects, consistent with our findings [34, 35]. Our participants reported local pain and tenderness at the injection site, consistent with Menni and his group's study that revealed the pain and soreness at the place where the vaccine was given [32]. Moreover, El-Shitany *et al*. [36, 37] did a trial in Saudi Arabia on a group of people who only got the Pfizer-BioNTech vaccine; they found that 70–80% of their group had local pain.

In our study, women were more likely than men to report side effects following vaccination; 48% of females reported side effects following the initial vaccine dose, compared to 23% of males; this difference was statistically significant ($P<0.0001$). Females are more likely than males to experience side effects following vaccination, according to prior research evaluating COVID-19 vaccines [36, 38, 39], such as influenza, the measles-mumps-rubella triple vaccine, attenuated Japanese encephalitis, and attenuated Dengue, indicated that females have more potent immune responses and that side effects are more common and severe [23, 40].

We noticed that the incidence of adverse events with the second vaccination dose was comparable to or slightly higher than with the first. In their studies, El-Shitany *et al*. [36] and Hatmal *et al*. [41] came to the same conclusion about the adverse side effects of the second dose of the vaccine. This observation could be understood in terms of an immune system reaction since specific cytokines are released by the immune system that causes inflammation in the vascular system, musculature, and many structures, as well as common

cold symptoms that continue for days following immunization [42]. Our findings indicate that the severity of side effects increased at the first and the second doses of COVID-19 vaccines compared to the boosters. This is inconsistent with the Centers for Disease Control and Prevention (CDC), which indicates that the intensity of adverse effects is elevated after the second dose [18].

Although our study is one of the few in Saudi Arabia to investigate the adverse effects of the three main confirmed COVID-19 vaccines, it has some limitations. The information was gathered using a self-administered web survey, which could lead to bias, especially with the age group, as internet access would be difficult for an older population to complete. Also, conducting society surveys for the long-term side effect of these vaccines with a larger cohort number of participants would help evaluate thromboembolic profiles and other commonly reported symptoms.

Conclusion

This study examined the short-term side effects of the Oxford-AstraZeneca, Pfizer-BioNTech, and Moderna COVID-19 vaccines. All three of these vaccines are approved for use in Saudi Arabia. We noticed several factors, such as gender, age, and underlying comorbidities, influencing the severity, susceptibility, and mortality of COVID-19. Most vaccinated populations in this study had tiredness, pain, and redness at the injection site, as well as a fever and headache, and these symptoms were more common in those who received the first and second doses of the vaccines. In addition, due to the adverse effects of immunizations, only a few people required medical attention or hospitalization. Compared to the Pfizer-BioNTech vaccine, the Oxford-AstraZeneca vaccine was significantly associated with fatigue and fever. A large-scale study is required to evaluate the vaccines' effectiveness in controlling and preventing SARS-CoV-2 infection and the long-term side effects.

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CONFLICT OF INTEREST: None

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ETHICS STATEMENT: The study was approved by the ethical committee of Taif University (Research number/44-014), Taif University, Taif City, Saudi Arabia. All participants provided written informed consent before their enrolment in the study. Informed consent was obtained from all subjects involved in the study.

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