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Susceptibility to COVID-19 Negatively Associated with Parental Consanguineous Marriage, A Case-Control Study

Mostafa Saadat[1*], Mohammad Hossein Zolaadl[2], Abdolrahim Asadollahi[3]

[1] Department of Biology, Faculty of Science, Shiraz University, Shiraz 71467-13565, Iran.

[2] Hafez Clinic, Moali'Abad Blvd, Shiraz, Iran.

[3] Department of Health Promotion & Gerontology, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran & The Middle East Longevity Institute in Abyad Medical Centre, Azmi Street, Abdo Center P.O. Box: 618, Tripoli, Lebanon

*Corresponding author: saadat@shirazu.ac.ir

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Abstract

Background: Marriage between biological relatives (second cousins and closer relatives) is called consanguineous marriage. Autosomal recessive diseases and several multifactorial traits are increased in the offspring of consanguineous marriages.

Aim: To investigate the relationship between parental consanguinity and COVID-19 susceptibility in their offspring, the present study was performed.

Methods: A total of 302 confirmed COVID-19 patients and 304 participants with other disease (as controls) were included in the study. Data on age, type of parental marriage, educational level, and history of underlying diseases of the participants were collected by a simple questionnaire through an interview conducted by a general practitioner.

Results: Statistical analysis showed that parental consanguinity was negatively associated with the risk of COVID-19 (OR=0.66, 95% CI=0.44-0.98, P=0.041). Using multivariable logistic regression analysis, parental consanguineous marriages significantly decreased the risk of COVID-19 after adjusting for age, education level, and the presence of underlying diseases such as diagnosed cardiovascular disease, hypertension, diabetes mellitus, and cancer (OR=0.60, 95% CI=0.40-0.90, P=0.014).

Conclusions: The present finding means that offspring of consanguineous marriages had a lower risk of COVID-19 than offspring of unrelated marriages.

Keywords: Consanguineous marriage, COVID-19, Case-control study.

INTRODUCTION

Marriage between biological relatives who are second cousins or closer is called consanguineous marriage. Several million people live in communities with a high prevalence of consanguineous marriage [1]. Numerous reports suggest that there are several primary reasons for the preference for

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consanguineous marriage in these communities, including lowering the cost of marriage, relative ease for the partners in finding a suitable spouse, backing the female status and improved relationships with in-laws, enhancing the likelihood of getting better care for people in old age [2]. It has been reported that marriages between biologically related individuals are more likely to be stable than marriages between unrelated individuals [3].

The socio-demographic and cultural background of a community directly influences the frequency of consanguineous marriages [4-8]. Several studies have shown that the prevalence of consanguineous marriages in Asian and African communities predominantly occurs between first cousins [1, 9-12]. Consanguineous marriages are associated with an increased risk of autosomal recessive diseases and many multifactorial traits in the offspring [1, 12-21].

On March 11, 2020, the World Health Organization declared coronavirus disease-2019 (COVID-19) is a new human pandemic due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of August 11, 2022, more than 592 million confirmed cases of COVID-19 and 6.4 million deaths have been reported worldwide. The unusual impact of COVID-19 on various aspects of the physical and mental health of patients causes this disease to have a major impact on the healthcare system of society [22, 23].

Primary immunodeficiency diseases, a genetically heterogeneous group, are associated with consanguineous marriages [24]. There is evidence that parental consanguineous marriage is a risk factor for some infectious diseases in humans [25, 26]. Approximately one-fifth of the world's population lives in countries where marriage with biological relatives is common. Therefore, for these countries, the association between consanguinity and susceptibility to COVID-19 is extremely important. To the best of our knowledge, there is only one ecological study that has examined the relationship between the mean of the inbreeding coefficient and the prevalence of COVID-19. Data analysis from 65 countries revealed a negative association between the prevalence of consanguineous marriages and the prevalence/mortality of COVID-19 [27]. Considering that there is no case-control or cross-sectional study on the association between parental consanguineous marriage and the risk of COVID-19, the present study was carried out.

METHODS

The present cross-sectional retrospective study was conducted from August 2021 to February 2022 in four medical centers in Shiraz city (Fars province, southwest Iran). Iran has a heterogeneous gene pool [9, 28, 29]; therefore, we selected the participants (patients and controls) from Persians (Caucasians) living in Shiraz. It should be noted that participants belonging to Azari, Arab, Lur, Turkmen, and Afghan ethnic groups were excluded from the study. The exclusion criteria were unwillingness to participate in the study, belonging to ethnic groups other than Persians, and incomplete questionnaires, especially about the type of parental marriages. Finally, a total of 302 confirmed COVID-19 patients and 304 participants with other diseases (as controls) were included in the study.

We used G-Power (www.psycho.uni-duesseldorf.de/aap/projects/gpower) software (version 3.1.3) to estimate the sample size. Assuming statistical power of 0.95, α=0.05 Lambda=14.88, and *df*=1, a

minimum of 325 total samples (including patients and controls) would be required to detect a small to medium effect size (=0.20) difference in the frequency of marital type between the COVID-19 patients and controls. The present study, with n=606, is more than adequately powered to detect an effect size of 0.20 for comparing the frequency of parental marital type between the study groups.

The present study was performed in accordance with the ethical codes of the Declaration of Helsinki and was approved by the local Ethics Committee. All participants gave informed consent in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki, 2013).

It has been established that underlying diseases such as cardiovascular disease, hypertension, diabetes mellitus, and cancer are important risk factors for susceptibility to SARS-CoV-2 infection and/or poor prognosis of COVID-19 (30-33). Data on age, parental marital status, education level, and history of underlying diseases of the participants were collected by a simple questionnaire through an interview conducted by a general practitioner.

The following variables were used for statistical analysis: Age (years), sex of participants [female (0) and male (1)], presence of underlying diseases [participants with no risk factor (0), participants with at least a positive history for diagnosed cancers, diabetes mellitus, cardiovascular diseases, and hypertension (1)], educational level [primary school (0), high school (1), and university (2)], and type of parental marriages [unrelated (0), second cousins (1), and first cousins (2)].

Independent two-sample t-test was used to compare age, and the chi-squared test was used to compare the gender of participants between COVID-19 and control groups. Logistic regression odds ratio (OR) and 95% confidence interval (95% CI) were used to analyze the difference between the study groups. In the next step, multivariable logistic regression analysis was used to investigate the relationship between type of parental marriage and susceptibility to COVID-19 in offspring after adjustment for possible confounders. Variables with $P<0.1$ in the univariable analysis were included in the multivariable model. Data analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA; version 25). $P<0.05$ was considered statistically significant.

RESULTS

Table 1 describes the description of the general characteristics of the study groups. A total of 302 (191 males, 111 females) COVID-19 patients and 304 (197 males, 107 females) controls were included in the study. There was no significant difference between cases and controls in terms of the gender of participants ($\chi^2=0.16$, df=1, P=0.690). The mean and standard deviation (SD) of age for the control and patient groups were 51.5 (10.8) and 48.6 (12.0) years, respectively. The difference was significant (t=3.12, df=604, P=0.002).

Among the parents of patients and controls, first-cousin marriage was the most common type of consanguineous marriage (80.1%). Considering the low prevalence of second-cousin marriages (25 out of 606), we pooled the data of first and second-cousin marriages for statistical analysis. Table 1 also shows that parental consanguineous marriages were negatively associated with the risk of COVID-19 (OR=0.66, 95% CI=0.44-0.98, P=0.041). After adjusting for the age of the participants, the same results were observed.

Table 1: Association between selected characteristics of participants with the risk of COVID-19

Characteristics	Controls	Cases	Crud OR	OR 95% CI	P	Adj. OR	OR 95% CI	P
Gender								
Males	197	191	1.0	-	-	1.0	-	-
Females	107	111	0.93	0.67-1.30	0.690	1.06	0.75-1.49	0.733
Educational levels								
Primary School	55	31	1.0	-	-	1.0	-	-
High School	157	136	1.53	0.93-2.52	0.090	1.48	0.90-2.44	0.121
University	92	135	2.60	1.55-4.35	<0.001	2.25	1.31-3.86	0.003
Underlying diseases								
Negative	199	191	1.0	-	-	1.0	-	-
Positive	105	111	1.10	0.79-1.53	0.569	1.47	1.01-2.13	0.041
Parental Consanguinity								
Unrelated marriages	230	249	1.0	-	-	1.0	-	-
Related marriages	74	53	0.66	0.44-0.98	0.41	0.65	0.44-0.98	0.041

Statistical analysis of the present data shows that the risk of COVID-19 was significantly associated with the level of education of the participants. Higher education was associated with higher risk of COVID-19 (χ^2 for trend =16.2, df=1, P<0.001). Similar results were obtained after adjustment for age. There was a significant association between the presence of underlying diseases and the risk of COVID-19 after adjusting for age (OR=1.47, 95% CI=1.02-2.12, P=0.041).

As mentioned in the Methods section, variables with P<0.1 in the univariable analysis were included in the multivariable model. Table 2 shows the results of the multivariable analysis. Our present results support that after adjusting for age, education level and underlying diseases, parental consanguineous marriages significantly decreased the risk of COVID-19 (OR=0.60, 95% CI=0.40-0.90, P=0.014). Finally, to exclude the potential influence of pooling first- and second-cousin marriages, statistical analysis was performed using data from first-cousin and unrelated marriages, and quite similar results were observed (Table 3).

Table 2: Multivariable logistic regressions analysis for associations between parental consanguinity and susceptibility to COVID-19 when adjusted for age, educational level and underlying diseases

Variables	Unstandardized coefficients		Wald	df	OR	95% CI	P
	B	Std. Error					
Constant	0.412	0.498	0.683	1	1.51	-	-
Biological related marriages *vs* Unrelated marriages	-0.509	0.208	6.026	1	0.60	0.40-0.90	0.014
Age (Years)	-0.020	0.008	5.626	1	0.98	0.96-0.99	0.018
Positive underlying diseases *vs* negative underlying diseases	0.446	0.193	5.352	1	1.56	1.07-2.28	0.021
High school *vs* primary school	0.414	0.257	2.587	1	1.51	0.91-2.50	0.108
University *vs* primary school	0.900	0.280	10.345	1	2.46	1.42-4.26	0.001

Table 3: Multivariable logistic regressions analysis for associations between parental consanguinity and susceptibility to COVID-19 when adjusted for age, educational level and underlying diseases

Variables	Unstandardized coefficients		Wald	df	OR	95% CI	P
	B	Std. Error					
Constant	0.565	0.514	1.207	1	1.76	-	-
Frist cousin marriages *vs* Unrelated marriages	-0.492	0.224	4.825	1	0.61	0.39-0.94	0.028
Age (Years)	-0.24	0.009	7.281	1	0.97	0.96-0.99	0.007
Positive underlying diseases *vs* negative underlying diseases	0.428	0.196	4.763	1	1.53	1.04-2.25	0.029
High school *vs* primary school	0.473	0.264	3.218	1	1.60	0.95-2.69	0.073
University *vs* primary school	0.928	0.287	10.428	1	2.52	1.44-4.44	0.001

DISCUSSION

Although not much time has passed since the first COVID-19 cases were reported, many studies have been conducted and published by researchers worldwide. Shortly after the World Health Organization announced a new pandemic, it became clear that several environmental factors influence the incidence and severity of the disease.

For genetic studies, researchers using ecological designs published their findings earlier than others. This was followed by case-control studies. Ecologic and case-control studies have shown that susceptibility

to COVID-19 and its outcome have a strong genetic basis [34-47]. Recently, genome-wide association studies introduced new candidate genes for the severity of COVID-19 [48, 49]. Therefore, it is well established that common genetic polymorphisms of the host can explain some of the individual differences for susceptibility to COVID-19, as well as, its clinical outcome.

The present study revealed that parental consanguineous marriage was negatively associated with the risk of COVID-19 in an Iranian population. This finding confirms a previous ecological study that reported a negative relationship between the frequency of consanguineous marriages and the prevalence/mortality of COVID-19 by analyzing data collected from 65 countries [27]. Previously, a negative association between susceptibility to HIV-1 infection and inbreeding coefficient has been reported [26], which is similar to our present finding.

Consanguineous marriages are known to increase homozygosity for low-frequency recessive alleles in gene pools. Therefore, the above association cannot be attributed to homozygosity for multiple low-frequency genetic polymorphisms in human gene pools. We know that consanguineous marriages increase the frequency of autosomal recessive traits at the expense of decreasing the frequency of dominant traits. Therefore, consanguineous marriages will reduce the frequency of the dominant trait in the population. In an unrelated marriage and in a consanguineous marriage with inbreeding coefficient F, the frequency of the dominant trait is equal to $p^2 + 2pq$ and $p^2 + 2pq - Fpq$, respectively (where p and q are the allelic frequencies of the dominant and recessive alleles, respectively). Therefore, it can be suggested that in the genetic polymorphisms related to COVID-19, the risk-causing alleles are functionally dominant, and for this reason the relationship between the risk of COVID-19 and consanguineous marriage is negative. This is a hypothesis that should be confirmed by future studies.

Finally, it should be noted that the present study has limitations. First, since COVID-19 is an infectious disease, adherence to health precautions and quarantine were very important and effective in reducing the risk of contracting the disease. This issue was not addressed in the study. Second, the risk of contracting many multifactorial traits and their relationship to genetics may be influenced by the gene pool. The association between a particular genetic polymorphism and the risk of a multifactorial disease may be statistically significant in some populations and not in others. Therefore, caution should be exercised in drawing definitive conclusions until the study is repeated in other populations. Third, it is possible that the severity of the disease and the frequency of infection were not the same in the patients. An issue that may affect the results and should be considered in future studies. Fourth, we did not examine the association study between genetic polymorphisms and COVID-19 susceptibility. This should be addressed in future studies.

In conclusion, the present study revealed that susceptibility to COVID-19 is significantly reduced in offspring of consanguineous marriages compared to offspring of unrelated marriages.

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and collecting the data, interpreting the data. All authors read and approved the final version of the manuscript.

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Availability of data and material: All data are presented in a Supplement file.

Declarations

Ethics approval and consent to participate: All participants were subjected to written consent in accordance with the Helsinki Declaration. The study had been approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1401.036).

Consent for publication: None

Competing interests: All authors declare that they have no competing interests.

Abbreviations

CI: confidence interval
COVID-19: Coronavirus disease-2019
df= Degree of freedom
F: Inbreeding coefficient
OR: odds ratio
p and q: Allelic frequencies
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SD: standard deviation
χ^2: Chi-square

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القابلية للإصابة بكوفيد-19 ترتبط سلباً بزواج الأقارب بين الوالدين، دراسة الحالات والشواهد

مصطفى سعادت[1]، محمد حسين نوالعدل[2]، عبدالرحيم أسداللهى[3]

[1] قسم الأحياء، جامعه شيراز، شيراز، إيران

[2] عيادة حافظ، معالي آباد، شيراز، إيران

[3] قسم تعزيز الصحة وعلم الشيخوخة، جامعه شيراز للعلوم الطبية، شيراز، إيران. معهد الشرق الأوسط لطول العمر بمركز الأبيض الطبي شارع عزمي مركز عبده، تريبولى، لبنان.

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الملخص

الخلفية والأهداف: الزواج بين الأقارب البيولوجيين يسمى زواج الأقارب. تزداد الأمراض الجسدية المتنحية والعديد من السمات متعددة العوامل في نسل زواج الأقارب.

وتهدف الدراسة العلاقة بين قرابة الوالدين وقابليه الإصابة بفيروس كورونا في نسلهم، تم إجراء هذه الدراسة.

منهجية الدراسة: تم تضمين ما مجموعه 302 مريضًا مؤكدًا بكوفيد-19 و304 مشاركين يعانون من أمراض أخرى (كعناصر تحكم) في الدراسة. تم جمع البيانات عن العمر ونوع زواج الوالدين والمستوى التعليمي وتاريخ الأمراض الأساسية للمشاركين من خلال استبيان بسيط من خلال مقابلة أجراها ممارس عام.

النتائج: أظهر التحليل الإحصائي أن قرابة الوالدين ارتبطت عكسياً بخطر الإصابة بكوفيد-19 (OR=0.66, 95% CI=0.44-0.98, P=0.041). باستخدام تحليل الانحدار اللوجستي متعدد المتغيرات، أدى زواج الأقارب بين الوالدين إلى انخفاض كبير في خطر الإصابة بكوفيد-19 بعد التعديل حسب العمر ومستوى التعليم ووجود الأمراض الأساسية مثل أمراض القلب والأوعية الدموية المشخصة وارتفاع ضغط الدم و السكري و السرطان (OR=0.60, 95% CI=0.40-0.90, P=0.014).

الاستنتاجات: تعني النتيجة الحالية أن نسل زواج الأقارب لديهم خطر أقل للإصابة بكوفيد-19 من نسل الزيجات غير ذات الصلة.

الكلمات الدالة: زواج الأقارب، كوفيد-19، دراسة الحالات والشواهد