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# The perceptiveness of the preventable measures and complications of osteoporosis in Saudi Arabia

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#### **ABSTRACT**

Background: Osteoporosis is a major public health problem worldwide. Osteoporosis prevention can be primary or secondary. This study assessed the level of perceptiveness about the preventable measures and complications of osteoporosis in KSA. Method: This was an observational cross-sectional study. Data was collected using an electronic, self-administered, structured questionnaire distributed in Saudi Arabia. SPSS 26 was used for data entry and data analysis. Results: The study included 2486 participants, 59.1% of whom were females and 45.3% were more than 30 years old. The vast majority (86.1%) knows what osteoporosis is and 83.1% think it is a serious condition. About 69% of participants reported women as a high-risk group and 92.2% said that osteoporosis increases the risk of fractures and 74.6% think osteoporosis can be prevented. About 54.1% take supplements containing calcium or vitamin D always or sometimes. Conclusion: The current study shows a moderate level of knowledge among the Saudi population about osteoporosis and its complications compared to other countries. And accordingly, it is essential to conduct explicit awareness programs on osteoporosis and its prevention programs.

Keywords: Osteoporosis, Perceptiveness, Bone strength, Saudi Arabia.

#### 1. INTRODUCTION

Osteoporosis, characterized by decreased bone density, deterioration of bone tissue and change of bone microarchitecture, can lead to compromised bone strength and an increased risk of fractures. The most prevalent cause is primary osteoporosis, which arises during the normal aging process associated with menopause and changes in sex hormones that occur with age (Sözen et al., 2017). On the other hand, secondary osteoporosis is frequently overlooked in patients with low bone density. The most common causative factors are vitamin D deficiency, hyperthyroidism, hyperparathyroidism, hypogonadism, some medications, solid organ transplantation in addition to



idiopathic hypercalciuria (Sözen et al., 2017).

The World Health Organization (WHO) stated the criteria to be used to assess the bone status and determine the fracture risk. These criteria consider the T score which compared the number of SDs (standard deviations) for which a patient's test score is above or below the average for the young adult group (positive T score) or below (negative T score). Bone density, also known as bone mineral density, is expressed as the ratio of two criteria: The T-score and the Z-score (BMD expected by a person's age and gender) (Sözen et al., 2017). Hip fracture is a serious complication of osteoporosis and it is linked to an increased risk of death and a worse quality of life. Up to 50% of patients experience lifelong mobility impairment (Sözen et al., 2017).

Prevention of osteoporosis should begin early in life. Primary prevention of growth and adolescence should aim to achieve high peak bone mass, adequate calcium intake, exercise and early diagnosis and treatment of potential skeletal malformations. Secondary prophylaxis aims to identify populations with low bone mass and multiple risk factors for osteoporosis-related fractures and to initiate multifactorial pharmacological and lifestyle-related interventions (Dontas and Yiannakopoulos, 2007).

About 200 million people suffer from osteoporosis and about 8.9 million fractures are caused by osteoporotic fractures (Khired et al., 2021; Sözen et al., 2017). Its prevalence is increasing and remains largely undiagnosed and untreated (Sözen et al., 2017). In the UK, one in every two women and one in every five men will experience a fracture after the age of 50. This causes significant health problems and costs health services around £2 billion each year (Sandhu et al., 2011). In the 1990s, it was realized that Saudi Arabia had a greater osteoporosis problem compared to other countries, with a reported prevalence of between 30% and 48% in the country (Sadat-Ali et al., 2012).

In 2019, a study was conducted in Egypt about osteoporosis and prevention methods among non-medical students. The study investigated the impact of explicit teaching programs on knowledge regarding osteoporosis and its prevention; they found that raising awareness among non-medical students aid in enhancing their knowledge regarding osteoporosis which helps in preventing the disease by avoiding osteoporosis risk factors (Farag and Hamed, 2019). Another study was performed in 2015 in Iran, aimed to use Health Belief Model (HBM) in the education of osteoporosis among primary school students. As a result, change in behaviours has been shown on account of understanding the risks of the disease (Jeihooni et al., 2017). One study was undertaken in Egypt in 2020 to evaluate the impact of the health belief model among childbearing women in regard to osteoporosis prevention, which displays a positive impact on promoting preventive behaviours such as increasing calcium intake and physical activity (Ali et al., 2020). An additional study that was performed in Iran in 2016 on high-school female students revealed that increasing awareness regarding osteoporosis disease will provide reduction and prevention of the disease (Moghimi et al., 2016). So, this study aimed to assess the level of perceptiveness about the preventable measures and complications of osteoporosis in KSA.

#### 2. METHODOLOGY

#### Study design/setting

The cross-sectional observational study was conducted in Saudi Arabia in the period from July to October 2022.

#### Data collection

Data was collected from 2486 adult Saudi males and females using a self-administered, electronic, designed, Arabic questionnaire that was distributed to the Saudi population as a link to Google form using social media platforms (e.g., Twitter, Instagram, Linkedin, WhatsApp, etc.,). Data was extracted as a Microsoft Excel sheet. Then, data was transferred to the Statistical Package of Social Science Software (SPSS) program, version 20 (IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY: IBM Corp.) to be statistically analyzed. Continuous data were statistically described in terms of median and IQR, while categorical data were described as frequencies and valid percentages.

#### Sample size

Considering a marginal error of 5%, a confidence level of 95% and considering maximum uncertainty (50% of positive responses) and a minimum of 377 participants were needed to be included in this study. The sample size was calculated using the Raosoft online sample size calculator.

#### 3. RESULTS

The study included 2486 participants, 59.1% were females and 40.9% were males. 45.3% of participants were more than 30 years old and 41.8% were 20-30 years old. 49.4% were single and 49.3% were married. 32.9% of study participants were from the western region of the kingdom, 32.1% were from the eastern region and 20.1% were from the central region. About 42.6% of participants

were overweight and 9.9% were obese. More details about the socio-demographic characteristics of participants are provided in (Table 1).

Table 1 Socio-demographic characteristics of participants (n=2486)

Parameter		No.	%
Gender	Male	1017	40.9
Gender	Female	1469	59.1
	Less than 20	321	12.9
Age	20 - 30 years old	1040	41.8
	More than 30	1125	45.3
Marital	Single	1229	49.4
status	Married	1226	49.3
Status	Widowed	31	1.2
	Southern	327	13.2
Residenc	Eastern	797	32.1
e region	North	45	1.8
	Western	818	32.9
	Central	499	20.1
Bmi	Underweight	62	2.5
	Normal	1117	44.9
	Overweight	1060	42.6
	Obese	247	9.9

Regarding knowledge of osteoporosis, 86.1% know what osteoporosis is and 83.1% think it is a serious condition. 69% of participants reported women as a high-risk group for osteoporosis, while 12.7% reported children. Causes and risk factors for osteoporosis were reported as 45.8% lack of movement, 43.2% menopause, 38.8% family history, 59.1% lack of sun exposure, 25.5% use of cortisone and 19.7% drinking caffeine. 92.2% reported that osteoporosis increases the risk of fractures. 43.2% think that calcium can be taken by drinking two glasses of milk a day. 74.5% think that dairy products have a role in preventing osteoporosis. 74.6% think that osteoporosis can be prevented. More details about the knowledge of participants of osteoporosis are provided in (Table 2).

Table 2 Knowledge of participants of osteoporosis (n=2486)

Parameter		No.	Percent
Know osteoporosis	Yes	2141	86.1
	No	345	13.9
Osta om omosis is a somious	Yes	2067	83.1
Osteoporosis is a serious health condition	No	183	7.4
neatti continui	Don't know	236	9.5
Diagraph and with	Yes	173	7.0
Diagnosed with osteoporosis	No	1896	76.3
	Don't know	417	16.8
Family history of	Yes	793	31.9
osteoporosis	No	1232	49.6
	Don't know	461	18.5
Highest risk group for osteoporosis	Children	315	12.7
	Men	101	4.1
	Women	1716	69.0
	Don't know	354	14.2
Know the symptoms of	Yes	1288	51.8

Lack of movement   1138   458     Menopause   1075   43.2     Family history   964   38.8     Thyroid gland activity   401   16.1     Use of cortisone   634   25.5     Not enough exposure to the sun   1468   59.1     Complications from other medications   754   30.3     Drinking a lot of coffee   489   19.7     All the above   671   27.0     Don't know   212   8.5     Don't know   212   8.5     Don't know   131   5.3     Calcium can be taken by drinking two glasses of milk a day   Don't know   656   26.4     All the above   676   27.0     Don't know   656   26.4     Don't know   1437   57.8     Dairy products have a role in preventing osteoporosis   No   229   9.2     Don't know   405   16.3     Pear osteoporosis can be prevented   Yes   1854   74.6     On't know   150   6.0     On't know   482   19.4     Osteoporosis can be prevented   Yes   1854   74.6     On't know   482   19.4     Osteoporosis can be prevented   Yes   1850   6.0     Don't know   482   19.4     Osteoporosis can be prevented   Yes   1854   74.6     Osteoporosis can be prevented   Yes   1850   6.0     On't know   482   19.4     Osteoporosis can be prevented   Yes   1854   74.6     Osteoporosis can be prevented   Yes   1850   6.0     On't know   482   19.4     Osteoporosis can be prevented   Yes   1850   6.0     Osteoporosis can b	osteoporosis	No	1198	48.2
Family history   964   38.8     Thyroid gland activity   401   16.1     Use of cortisone   634   25.5     Not enough exposure to the sun   Complications from other medications   Drinking a lot of coffee   489   19.7     All the above   Don't know   212   8.5     Ves   Don't know   212   8.5     Ves   Don't know   131   5.3     Calcium can be taken by drinking two glasses of milk a day   Don't know   Month of the complications of the complex of the co	1	Lack of movement	1138	45.8
Family history   964   38.8     Thyroid gland activity   401   16.1     Use of cortisone   634   25.5     Not enough exposure to the sun   Complications from other medications   Drinking a lot of coffee   489   19.7     All the above   Don't know   212   8.5     Ves   Don't know   212   8.5     Ves   Don't know   131   5.3     Calcium can be taken by drinking two glasses of milk a day   Don't know   Month of the complications of the complex of the co		Menopause	1075	43.2
Use of cortisone			964	38.8
Causes and risk factors for osteoporosis (Overlap present)         Not enough exposure to the sum         1468         59.1           Complications from other medications         754         30.3           Drinking a lot of coffee         489         19.7           All the above         671         27.0           Don't know         212         8.5           Yes         2293         92.2           No         62         2.5           Don't know         131         5.3           Calcium can be taken by drinking two glasses of milk a day         No         757         30.5           And the above description of the incidence of fractures         No         757         30.5           Acalcium can be taken by drinking two glasses of milk a day         No         757         30.5           Acalcium can be taken by drinking two glasses of milk a day         No         757         30.5           Becommended daily amount of calcium for women over the age of fifty         1200 milligrams every day         476         19.1           500 milligrams every day age 50         13.3         11.5         18.5         74.5           Dairy products have a role in preventing osteoporosis         No         229         9.2           No         229 <td< td=""><td></td><td>Thyroid gland activity</td><td>401</td><td>16.1</td></td<>		Thyroid gland activity	401	16.1
Not enough exposure to the sun   1468   59.1		Use of cortisone	634	25.5
(Overlap present)         the sun         754         30.3           Complications from other medications         754         30.3           Drinking a lot of coffee         489         19.7           All the above         671         27.0           Don't know         212         8.5           Yes         2293         92.2           No         62         2.5           Don't know         131         5.3           Calcium can be taken by drinking two glasses of milk a day         No         757         30.5           No         759         30.5		Not enough exposure to		59.1
Complications from other medications		the sun	1468	
All the above   Don't know   212   8.5	(Overlap present)	_	754	30.3
All the above   Don't know   212   8.5		Drinking a lot of coffee	489	19.7
Osteoporosis increases the incidence of fractures         Yes         2293         92.2           No         62         2.5           Don't know         131         5.3           Calcium can be taken by drinking two glasses of milk a day         Yes         1073         43.2           No         757         30.5           Don't know         656         26.4           1200 milligrams every day         476         19.1           500 milligrams every day         330         13.3           It's too late to increase your calcium intake after age 50         243         9.8           Dairy products have a role in preventing osteoporosis         Yes         1852         74.5           No         229         9.2           Don't know         405         16.3           Yes         1944         78.2           Fear osteoporosis         No         329         13.2           Don't know         213         8.6           Osteoporosis can be prevented         No         150         6.0		_	671	27.0
Osteoporosis increases the incidence of fractures         No         62         2.5           Don't know         131         5.3           Calcium can be taken by drinking two glasses of milk a day         Yes         1073         43.2           No         757         30.5           Don't know         656         26.4           1200 milligrams every day         476         19.1           500 milligrams every day         330         13.3           It's too late to increase your calcium intake after age 50         243         9.8           Dairy products have a role in preventing osteoporosis         Yes         1852         74.5           No         229         9.2           Don't know         405         16.3           Yes         1944         78.2           Fear osteoporosis         No         329         13.2           Don't know         213         8.6           Osteoporosis can be prevented         Yes         1854         74.6           No         150         6.0		Don't know	212	8.5
No	0.1	Yes	2293	92.2
Don't know	=	No	62	2.5
No   757   30.5     A day   Don't know   656   26.4     Recommended daily amount of calcium for women over the age of fifty   Don't know   1437   57.8     Dairy products have a role in preventing osteoporosis   Don't know   405   16.3     Fear osteoporosis can be prevented   Pon't know   1854   74.6     Osteoporosis can be prevented   No   757   30.5     No   264   26.4     1200 milligrams every day   476   19.1     1500 milligrams every day   330   13.3     15's too late to increase your calcium intake after age 50     Don't know   1437   57.8     Yes   1852   74.5     No   229   9.2     Don't know   405   16.3     Yes   1944   78.2     No   329   13.2     No   150   6.0     No   150   6.0	incidence of fractures	Don't know	131	5.3
Don't know   656   26.4	Calcium can be taken by	Yes	1073	43.2
1200 milligrams every day	drinking two glasses of milk	No	757	30.5
Solo milligrams every day   330   13.3     It's too late to increase   your calcium intake after   age 50     Don't know   1437   57.8     Dairy products have a role in preventing osteoporosis   Pear osteoporosis     Fear osteoporosis   No   329   13.2     Don't know   213   8.6     Yes   1854   74.6     No   150   6.0     Osteoporosis can be prevented   No   150   6.0     Osteoporosis   13.3     It's too late to increase   your calcium intake after   age 50     Pon't know   1437   57.8     Yes   1852   74.5     No   229   9.2     Don't know   405   16.3     Yes   1944   78.2     No   329   13.2     Osteoporosis can be prevented   No   150   6.0	a day	Don't know	656	26.4
It's too late to increase your calcium intake after age 50		1200 milligrams every day	476	19.1
18 too late to increase   your calcium intake after   243   9.8     39.8   39.8   39.8     39.8   39.8     39.8     39.8     39.8     39.8     39.8     39.8     39	Dogommondod doile	500 milligrams every day	330	13.3
women over the age of fifty         your calcium intake after age 50         243         9.8           Don't know         1437         57.8           Pairy products have a role in preventing osteoporosis         Yes         1852         74.5           No         229         9.2           Don't know         405         16.3           Yes         1944         78.2           No         329         13.2           Don't know         213         8.6           Yes         1854         74.6           No         150         6.0		It's too late to increase		
Age 50   Don't know   1437   57.8		your calcium intake after	243	9.8
Dairy products have a role in preventing osteoporosis         Yes         1852         74.5           No         229         9.2           Don't know         405         16.3           Yes         1944         78.2           No         329         13.2           Don't know         213         8.6           Yes         1854         74.6           No         150         6.0	women over the age of mity	age 50		
No         229         9.2           Don't know         405         16.3           Yes         1944         78.2           Fear osteoporosis         No         329         13.2           Don't know         213         8.6           Yes         1854         74.6           Osteoporosis can be prevented         No         150         6.0		Don't know	1437	57.8
No   229   9.2	Dairy products have a role	Yes	1852	74.5
Don't know	, .	No	229	9.2
No         329         13.2           Don't know         213         8.6           Osteoporosis can be prevented         Yes         1854         74.6           No         150         6.0	ni bie seittiik osteoborosis	Don't know	405	16.3
Don't know         213         8.6           Yes         1854         74.6           No         150         6.0		Yes	1944	78.2
Osteoporosis can be prevented Yes 1854 74.6  No 150 6.0	Fear osteoporosis	No	329	13.2
Osteoporosis can be prevented  No 150 6.0		Don't know	213	8.6
prevented No 150 6.0	Ostooporosis can bo	Yes	1854	74.6
Don't know 482 19.4	*	No	150	6.0
	preventeu	Don't know	482	19.4

Table 3 and Figure 1 show that 84% of the participants consult an osteoporosis doctor if necessary. Only 13.1% attended educational programs or workshops on osteoporosis. 9.2% done density test for osteoporosis. 53.3% measured calcium or vitamin D level in the blood (11.8% of them had a low level of calcium and vitamin D, while 66.8% were within the normal range).

Table 3 Attitude of participants of osteoporosis (n=2486)

Parameter		No	Percent
Consult an osteoporosis doctor if necessary	Yes	2088	84.0
	No	217	8.7
	Don't know	181	7.3
Attended an educational program or workshops on osteoporosis	Yes	325	13.1
	No	2081	83.7
	Don't know	80	3.2
Done density test for osteoporosis	Yes	237	9.5
	No	2069	83.2

	Don't know	180	7.2
Measured level of calcium or	Yes	1324	53.3
vitamin D in the blood	No	984	39.6
Vitantini D in the blood	Don't know	178	7.2
	High levels of calcium and vitamin D	67	4.7
If yes, measurements refer to	Low level of calcium and vitamin D	158	11.8
	Low calcium level only	74	5.6
	Low level of vitamin D only	146	11
	Within the normal range	881	66.8

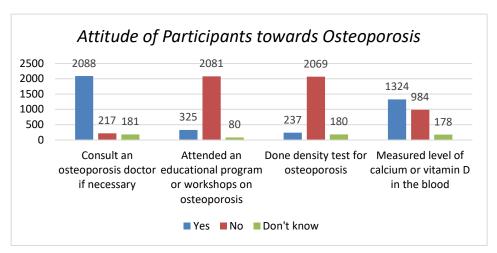
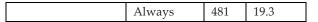


Figure 1 Attitude of participants towards osteoporosis

In Table 4 and Figure 2, 12.8% and 41.3% take any type of supplement containing calcium or vitamin D always or sometimes, respectively. 11.1% are always exposed to sunlight before 10:00 am. 19.3% eat foods that are rich in vitamin D and calcium.

Table 4 Practice of participants towards osteoporosis (n=2486)

Parameter		No.	Percent
Take any type of	Never	626	25.2
supplement	Rarely	515	20.7
containing calcium	Sometimes	1026	41.3
or vitamin D	Always	319	12.8
	Never	462	18.6
Exposure to the sun	Rarely	784	31.5
before 10:00 am	Sometimes	963	38.7
	Always	277	11.1
	Never	317	12.8
Practice exercise	Rarely	709	28.5
Fractice exercise	Sometimes	1080	43.4
	Always	380	15.3
Eat foods rich in	Never	102	4.1
calcium and	Rarely	387	15.6
vitamin D	Sometimes	1516	61.0



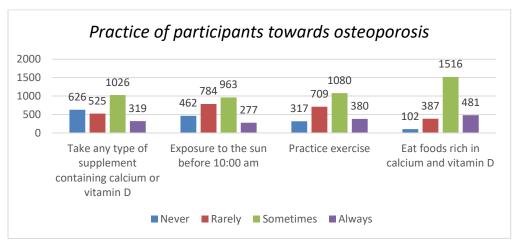


Figure 2 Practice of participants towards osteoporosis

# 4. DISCUSSION

This cross-sectional study aims to assess the perceptiveness about the preventable measures and complications of osteoporosis in KSA. In our study, 86.1% of participants have knowledge of osteoporosis. This was higher than reported in previous literature as a noticeable lack of understanding of osteoporosis among young adults and adolescents was discovered in one review by Chin et al., (2018) which included 34 studies from around the world. Even in groups that are ostensibly more likely to be knowledgeable about osteoporosis, like medical students, some authors reported less knowledge than ideal in this area (Bilal et al., 2017; Khired et al., 2021; Senthilraja et al., 2019). In a different study, postmenopausal women, a crucial population with a higher risk of osteoporosis, were found to be unaware of the condition (Suriawati et al., 2016). The discrepant results may be attributed to variations in participant age, education and cultural background. Low literacy rates and low socioeconomic status, which put them at risk for osteoporosis and its complications, may be to blame for the low level of knowledge.

In comparison to other risk factors, awareness of family history and its link to osteoporosis was lower (56.1%), which is higher than the rate at a primary healthcare facility in Dirab, Riyadh, Saudi Arabia, where only 22% of the female patients acknowledged family history as a risk factor (Al-Shahrani et al., 2010). Participants in Qatar received a score that was lower than ours (36.0%) (Al-Muraikhi et al., 2017). Only 22% of 622 women surveyed in New Zealand in 2007 knew that participants with osteoporosis family history are more susceptible to developing it (Hurst et al., 2007).

Understanding the seriousness of osteoporosis is necessary for modifying certain health behaviors related to diet and physical activity. Getting sufficient daily calcium intake is important to minimize osteoporosis risk (Ahmadieh et al., 2018; Bilal et al., 2017). In our study, 83.1% think it is a serious condition and 74.5% think that dairy products have a role in preventing osteoporosis. According to a study, 83% of participants knew the recommended daily allowance for calcium and 91% named sardines and broccoli as calcium-rich foods (Borer, 2005). These results were higher than those of a study conducted on Saudi female college students, who scored 68% and 57%, respectively. This difference in results may be due to the different age groups used in our study (Alshareef et al., 2018). Just over half of the participants in the aforementioned New Zealand study recognized broccoli as a source of calcium and only a small percentage of Qatari women were aware that sardines and broccoli are high in calcium in another study (Al-Muraikhi et al., 2017). This was in contrast to a study conducted in Egypt that revealed low perceived severity, possibly because the majority of respondents were premenopausal housewives who may not have been motivated to learn more about osteoporosis (Mortada et al., 2020). This underlines how crucial it is to understand calcium's non-dairy sources, particularly for those who can't tolerate lactose or follow a vegan diet.

In our study, 92.2% of participants reported that osteoporosis increases the incidence of fractures. This was higher than the results reported in another study, as three-quarters of the respondents in this analysis agreed that osteoporosis and fractures are related (Alrashidy, 2021). A study from southern India reported comparable percentages (Senthilraja et al., 2019). Notably, 1 in 4 people in our sample continues to deny that osteoporosis increases the risk of fractures. Simply increasing public education efforts could help with this.

Given that estrogen deficiency plays a role in bone loss, postmenopausal women are particularly at risk for osteoporosis. Two hundred million women are thought to have postmenopausal osteoporosis worldwide and 30 to 50 percent of these women are

expected to experience a clinical fracture (Johnell and Kanis, 2006). A sensible and successful treatment for osteoporosis in peri- and early postmenopausal women is hormone replacement therapy (Gambacciani and Levancini, 2014). In our study, 69% of participants reported women as a high-risk group for osteoporosis.

As for the prevention of osteoporosis, 74.6% of our participants think that osteoporosis is preventable. 12.8% of participants always take supplements containing calcium or vitamin D for the prevention of osteoporosis. In another study contradicting our results, only a small percentage of respondents thought that regular exercise and a diet high in calcium could prevent osteoporosis. These results concur with other studies' results (Saw et al., 2003). The subjects did not regularly engage in osteoporosis prevention strategies because only 37.4% consumed dairy products and 15.0% took calcium supplements. Insecurities about calcium food sources and supplements, worries about weight gain and the fat and cholesterol content of some calcium-rich foods are some of the potential obstacles to obtaining an adequate calcium intake, according to earlier studies (Chan et al., 2019; French et al., 2008). According to these reports, the lack of knowledge hampers correct practice. It is crucial to set up programs that inspire people to hold the proper beliefs in order to get past obstacles in preventive measures. Correct, non-conflicting information is helpful in promoting a healthy attitude toward exercise, calcium intake and lowering osteoporosis susceptibility. It is preferable for the attending clinician to receive this information than for the women to look for it independently.

# 5. CONCLUSION

In conclusion, the study shows a moderate level of public knowledge about osteoporosis in Saudi Arabia, compared to previously reported figures worldwide. This demonstrates the need for prevention programs and awareness campaigns that should concentrate on high schools and universities so that individuals can determine whether they are at higher risk of osteoporosis and as a result, alter their health-related behaviors.

# Acknowledgement

We thank the participants who were all contributed samples to the study.

#### Authors' contributions

Rayan Alamri: Conceptualization, methodology and writing-original draft.

Afrah Alharthi: Conceptualization, methodology, reviewing and editing and data collection.

Atheer Ismail: Conceptualization, methodology, writing-reviewing and editing, visualization and data collection.

Mohammed Alamri: Conceptualization, methodology, reviewing and editing and data collection.

Eyad Alfaqih: Conceptualization, methodology, reviewing and editing and supervision.

Abdulmohsen Alghamdi: Conceptualization, methodology, writing- reviewing and editing and formal analysis.

Abdulkareem Almalki: Conceptualization, methodology, writing- original draft, project administration and supervision.

#### Ethical approval

Approval was obtained from Health Services Department for Armed Forces Scientific Research Center Research Ethics Committee project application number (2022-627).

#### Informed consent

Written informed consent was obtained from all participants included in the study.

# **Funding**

This study has not received any external funding.

# Conflict of interest

The authors declare that there is no conflict of interests.

#### Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

# **REFERENCES AND NOTES**

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