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Vitamin D status among adults (18-65 years old) attending Primary Health Care Centers in Qatar, 2017: An Analysis of Electronic Medical Records

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029334
Article Type:	Research
Date Submitted by the Author:	22-Jan-2019
Complete List of Authors:	Zainel, A.Jaleel; Primary Health Care Corporation, Clinical Affairs Qotba, Hamda; Primary Health Care Corporation, Clinical Affairs, Research Department Al Nuaimi , Ahmed ; Primary Health Care Corporation, Research Department, Clinical Affairs Directorate Syed , Mohamed; Primary Health Care Corporation, Research Department, Clinical Affairs Directorate
Keywords:	Vitamin D, Adults, Chronic disease, Prevalence, Qatar

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Vitamin D status among adults (18-65 years old) attending Primary Health Care Centers in Qatar, 2017: An Analysis of Electronic Medical Records

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Abstract

Objectives To investigate the prevalence of vitamin D deficiency among subjects attending primary health care facilities in Qatar and to assess the association between vitamin D deficiency and some medical conditions in people aged 18-65 years old.

Setting the all-23 health centers providing primary health care services in the State of Qatar.

Participants 102,342 clients aged between 18 and 65 years old with a valid serum vitamin D test result during the year 2017.

Outcome measures Cut-off values used to diagnose severe vitamin D deficiency was having a serum level <10 ng/ml (<25 nmol/L) of vitamin D, to diagnose vitamin D deficiency a serum level of <20 ng/ml (<50 nmol/L) and used a level of <30 ng/ml (<75 nmol/L) to diagnose the vitamin D insufficiency.

Results The prevalence rate of severe vitamin D deficiency reached 14.1% among subjects without evidence on receiving any type of vitamin D therapy while vitamin D deficiency reached 71.4% and vitamin D insufficiency reached 92.7% among the same group. None of the five chronic conditions explored in the current study (diabetes, hypertension, asthma, stroke and cardiovascular disease) had an obvious association with severe vitamin D deficiency status in bivariate analysis. However, the multivariate modelling showed that (adjusting for age, gender, body mass index and nationality and each of the included chronic conditions) hypertension, cardiovascular diseases and stroke increased the risk of having severe Vitamin D deficiency status.

Conclusion: Although not comprehensive and nationally representative, this study is suggestive of a higher prevalence of vitamin D deficiency among young adults, females, Qatari nationality and those with higher body mass index. Multivariate modelling showed that hypertension, cardiovascular diseases and stroke increased the risk of having severe vitamin D deficiency status.

Key words: Vitamin D, Adults, Chronic disease, Prevalence, Qatar

Strengths and limitations of this Study

- An advantage of this study is that it used readily available data, which required fewer resources compared to collecting new data.
- The current retrospective study was not able to demonstrate temporality, as the predisposing factors or determinants of vitamin D deficiency cannot identified with high degree of confidence except through an observational longitudinal study.
- Difference in the applied diagnostic criteria and laboratory cut-off values in identification of vitamin D deficiency and insufficiency across different studies may limits the ability of a precise comparison.
- Selection bias as there is no randomization in sampling; in addition to that, included population may be at risk of vitamin D deficiency as usually test requesting done for defined clients according to special criteria and indications. Therefore, not all people had equal chances to be included in this study.
- Kind of data is relatively poor, as many data are not recorded or completed in the electronic medical records (EMR).

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Introduction

Vitamin D is a steroid vitamin, which in together with other physiological factors, controls the metabolism of calcium and phosphorus. There are different sources of vitamin D. Mainly exposure to the sun where ultraviolet B radiation (wavelength 290 - 315 nm) promotes synthesis of vitamin D from 7-dehydrocholesterol in the skin[1]. The influence of diet on vitamin D status is poor accounting for 3.7 - 5.9 µg or 148 - 236 International Unit daily[2]. The major dietary sources of vitamin D come from milk and plant-based beverages and from optional fortification of fruit juices and yoghurts[3].

Vitamin D deficiency can have serious consequences such as failure of the bones to grow potentially leading to rickets in children and osteoporosis or osteomalacia in adults[4, 5]. It is a widely spread micronutrient problem globally. In Qatar, a prevalence rate of around 90% was reported[6, 7].

Many factors are associated with reduction in the serum level of vitamin D in adults. These factors mainly include: advancing age, female gender, clothing style, season, socio-economic status, urban living, dark skin and body mass index (BMI)[8, 9]. In a Saudi study, vitamin D deficiency was reported to be common among older men with no education and sedentary lifestyle sampled during summer and spring[10]. A study conducted in Morocco, concluded that one of the main determinants of hypovitaminosis D was age > 55 years [11]. A systematic review showed increase in the prevalence of vitamin D deficiency with age[6]. Joergensen and colleagues revealed that vitamin D level was not associated with gender[12]. While a study conducted in Qatar revealed that the mean overall vitamin D level was lower in females compared to males[7]. This gender inequality was also reported by another study from Emirates[13].

Clothing which covers all parts of the body, spending time outdoors for less than 30 minutes/day and urban living have shown negative effects on the level of serum vitamin D[14, 11]. Spending more than 1 hour outdoors was independently associated with higher vitamin D levels in a cross-sectional study[15].

Vitamin D deficiency was common among obese men with no education and sedentary lifestyle sampled during summer and spring in a Saudi cross-sectional study[10]. This observation was reported in another study on a group of healthy, white, obese medical school personnel, which showed that BMI was inversely correlated with serum vitamin D3 concentrations[9].

In addition to the direct complications, the deficiency of vitamin D affecting bone growth and development causing bone deformities in children and bone diseases in adults[4, 5]. Its deficiency related to many other diseases and conditions, which may deteriorate or improve according to the level of serum vitamin D. Diabetes mellitus is more likely with vitamin D deficiency, as vitamin D acts through several mechanisms on glucose metabolism. Vitamin D is known to act on insulin producing cells (β cells) in the pancreas to produce more insulin, it acts on the muscle and fat cells to improve insulin action by reducing insulin resistance as well as vitamin D indirectly improves insulin production and its action by improving the level of calcium inside the cells[12, 16, 17, 18]. In a study from Spain, vitamin D concentrations correlated negatively with total cholesterol and LDL cholesterol levels[15]. Colorectal cancer mortality was inversely related to serum vitamin D level, with levels 80 nmol/L or higher associated with a 72% risk reduction compared with lower than 50 nmol/L[2]. A cross-sectional study showed a positive correlation between bone mineral density values at both lumbar spine (L1-L4) and neck femur and serum vitamin D levels, respectively[10].

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While high prevalence of vitamin D deficiency has been reported as a public health concern globally, reliance on a single cut-off value to define vitamin D deficiency or insufficiency is problematic because of the wide individual variability of the functional effects of vitamin D and interaction with calcium intakes[19]. In studies, cut-off values are often chosen when there is evidence of decreased risk for selected end-points for subjects with serum levels greater than that cut-off value. These end-points include: fractures, cardiovascular diseases, colorectal cancer, diabetes, depressed mood, cognitive decline and death[20]. Some published studies demonstrated vitamin D deficiency can be diagnosed when the level of serum vitamin D is <25 nmol/L (<10 ng/ml)[21]. Others defined deficiency as serum vitamin D <50 nmol/L (<20 ng/ml)[20]. The desirable level for an adult is > 75 nmol/L (>30 ng/ml). A U shape relation between serum vitamin D level and adverse outcome was noticed. A level of >250 nmol/L (>100 ng/ml) invites problems[21]. A level of 20-30 ng/ml of serum vitamin D is known as insufficient or suboptimal vitamin D status[21].

This study aimed to investigate the prevalence of vitamin D deficiency among adult subjects attending primary health care facilities. In addition, it assessed the association between vitamin D deficiency and some medical conditions (diabetes, asthma, hypertension, cardiovascular diseases, and stroke) in people aged 18-65 years old. The current study provides a much-needed snapshot of the extent of problem in the State of Qatar.

Methods

Study design: Cross-sectional study.

Study setting: Qatar, a peninsular Arab country with a high-income economy backed by the world's third-largest natural-gas reserves, has been developing investing significantly on its health care system. This includes a publically funded primary health care (PHC) service delivered by the Primary Health Care Corporation (PHCC) with which is the largest primary care provider publically funded by the State of Qatar with 23 health centers at the time of writing this paper (all accredited by Accreditation Canada International) and distributed across the country on three geographical regions.

Study population: A total of 102,342 EMR extracted from PHCC's CERNER system (official EMR system) for clients aged between 18 and 65 years old with a valid serum vitamin D test result during the year 2017.

Study variables: The outcome variable is vitamin D deficiency which is tested at three cut-off values. The independent (exposure) variables included age, gender, nationality, BMI, and a list of selected chronic medical conditions. These include: diabetes, hypertension, asthma, stroke and cardiovascular disease.

Data Collection: Data were extracted from the PHCC's EMR system for the defined study population. The data was for a time period of 1st January to 31st December 2017.

Data analysis: The Statistical Package for Social Sciences (IBM-SPSS Ver 23) was used for data analysis. Descriptive Statistics were done first. Multivariate Discriminant Analysis was used to predict a severe vitamin D status based on age, nationality, gender, BMI and co-morbid chronic conditions. The multivariate modelling helps to control the confounding effect of all the explanatory variables included in the model. No test of significance was needed since all the population was analyzed.

A review of the literature suggests many cut-off values for defining vitamin D inadequacy. For the purposes of this study, severe vitamin D deficiency was defined as having a serum level of <10 ng/ml,

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vitamin D deficiency was defined as having a serum level of <20 ng/ml and vitamin D insufficiency was defined as having a serum level of <30 ng/ml.

Quality control measures: In the preparation phase of the study, the authors performed an extensive review of literature and consulted with academic experts in community medicine and other related fields. The principle researchers were responsible for data collection in collaboration with the EMR management team. Standardized methods of blood collection and automated measures for blood analysis were used to ensure reliability of the study results.

Ethical Consideration: The study presented minimal risk of harm to its subjects, and the data collected were anonymized. None of the subjects' personal information was revealed to the research team. Overall, the study was conducted with integrity according to generally accepted ethical principles and was approved by the PHCC's Research Committee.

Patient and Public Involvement: Patients' priorities, experience and preferences were not gathered nor were they involved in designing the study. The team of health information management (HIM) in PHCC supported in data collection. There are no plans to disseminate results to the study participants directly as they are already anonymized.

Results

The results presented in this chapter were based on the analysis of 102,342 primary health care clients (adults between 18 and 65 years old) with a valid serum vitamin D test result during the year 2017 as shown in **table 1**.

Table 1: frequency distribution of the total study sample with an available recorded value for serum Vitamin D during the study period of 2017

	N	%
Age group in years		
18-29	23,348	22.8
30-39	30,889	30.2
40-49	24,736	24.2
50-65	23,369	22.8
Total	102,342	100.0
Gender		
Female	67,393	65.9
Male	34,946	34.1
Total	102,339	100.0
Nationality		
other nationalities	72,314	70.7
Qatari	30,028	29.3
Total	102,342	100.0
received vitamin D therapy before the last serum Vitamin D test		
no	70,818	68.9
yes	31,903	31.1
Total	102,721	100.0
BMI Measurement in latest visit		

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Acceptable (<25)	18,108	23.2
overweight (25-29.9)	26,523	34.0
grade 1 or low risk obesity (30-34.9)	19,549	25.1
grade 2 or moderate risk obesity (35-39.9)	9,008	11.6
obesity grade 3 (morbid obesity) (40+)	4,779	6.1
Total	77,967	100.0

Figure 1 demonstrates the prevalence rate of vitamin D insufficiency, deficiency and severe deficiency among treated and non-treated study subjects.

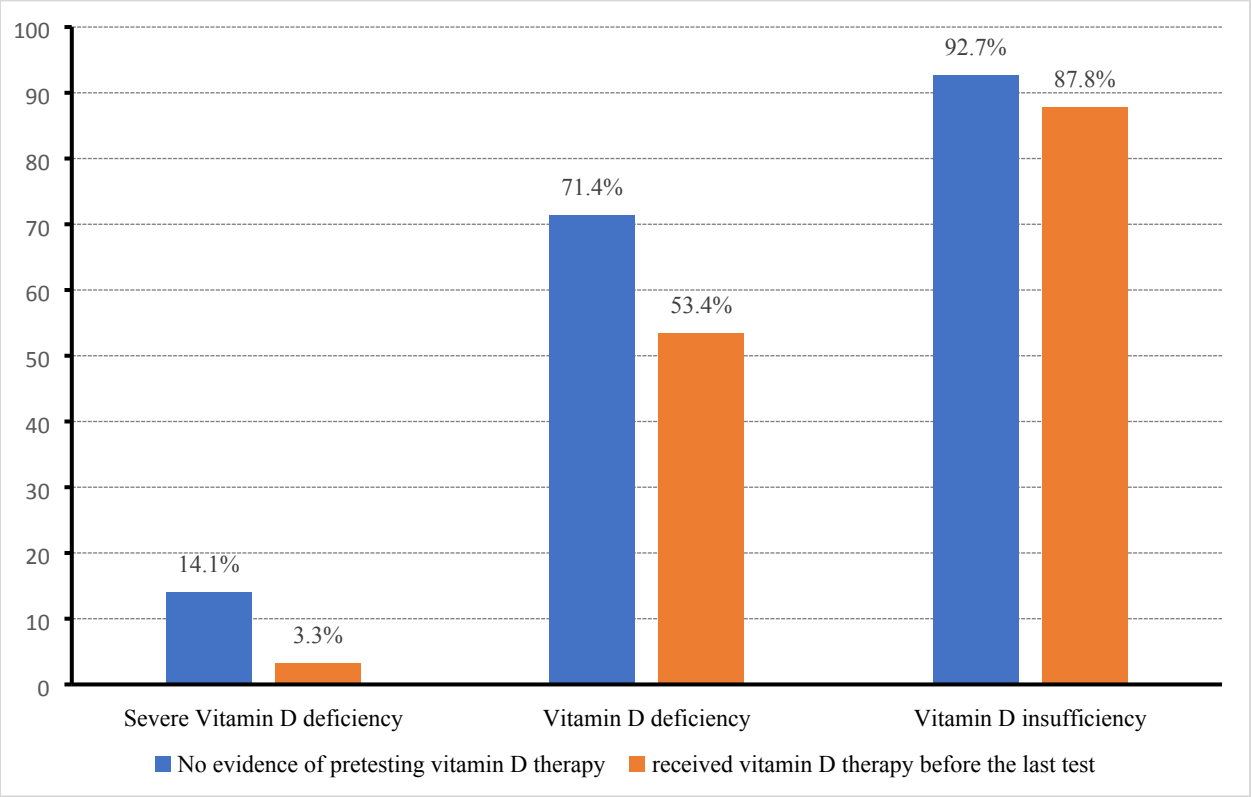

Figure 1: The prevalence rate of selected outcomes based on different serum Vitamin D cut-off values among subjects with no evidence of Vitamin D therapy before testing compared to those who received such therapy

As shown in **table 2**, the relation between sociodemographic factors and vitamin D status is relatively affected by the cut-off values of vitamin D. **Table 2** is also showing that there is no obvious or consistent seasonal variations in prevalence rate of vitamin D deficiency at any of the three tested cut-off values were observed in the current study.

From studying **table 2**, it was shown that age had a strong association with deficiency status of vitamin D. In addition, age is known to be associated with BMI and other risk factor studied. Therefore, age qualifies as a strong confounder for any association between explanatory variables tested and the deficiency status. A stratified analysis, adjusting for age as a confounder would be a good solution to adjust for this undesired confounding effect.

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Table 2: The prevalence of selected outcomes based on different serum vitamin D cut-off values for subjects with no evidence of vitamin D therapy before testing stratified by sociodemographic variables

	Total	Severe Vitamin D deficiency		Vitamin D deficiency		Vitamin D insufficiency	
	N	N	%	N	%	N	%
Age group in years							
18-29	17,862	4,712	26.4	14,610	81.8	17,036	95.4
30-39	22,788	2,951	12.9	16,565	72.7	21,276	93.4
40-49	16,808	1,536	9.1	11,482	68.3	15,522	92.3
50-65	13,234	775	5.9	7,847	59.3	11,711	88.5
Gender							
Female	44,773	7,459	16.7	32,649	72.9	41,328	92.3
Male	25,916	2,514	9.7	17,852	68.9	24,214	93.4
Nationality							
other nationalities	51,158	6,277	12.3	36,344	71	47,905	93.6
Qatari	19,534	3,697	18.9	14,160	72.5	17,640	90.3
Season (year quarter) of testing for serum Vit D							
First quarter	14,691	2,085	14.2	10,697	72.8	13,753	93.6
Second quarter	15,127	1,807	11.9	10,682	70.6	14,092	93.2
Third quarter	18,447	2,860	15.5	13,545	73.4	17,183	93.1
Fourth quarter	22,427	3,222	14.4	15,580	69.5	20,517	91.5
BMI (Kg/m^2) Measurement in latest visit							
Acceptable (<25)	13,079	2,191	16.8	9,224	70.5	11,997	91.7
overweight (25-29.9)	17,606	2,257	12.8	12,307	69.9	16,205	92.0
grade 1 or low risk obesity (30-34.9)	11,987	1,642	13.7	8,676	72.4	11,134	92.9
grade 2 or moderate risk obesity (35-39.9)	5,313	825	15.5	4,042	76.1	4,967	93.5
obesity grade 3 (morbid obesity) (40+)	2,756	488	17.7	2,169	78.7	2,585	93.8

After adjusting for age group, the prevalence of severe vitamin D deficiency among subjects with no evidence of therapy is showing in **table 3**.

Table 3: The prevalence of severe Vitamin D deficiency (<10 ng/ml) among subjects with no evidence of vitamin D therapy before testing by selected explanatory variables after adjusting for age group

	Total	Severe Vitamin D deficiency (<10 ng/ml)	
	N	N	%
Gender			
18-29 years of age			
Female	13,712	3,900	28.4
Male	4,150	812	19.6

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	Total	Severe Vitamin D deficiency (<10 ng/ml)	
	N	N	%
30-39 years of age			
Female	15,121	2,190	14.5
Male	7,666	761	9.9
40-49 years of age			
Female	9,528	999	10.5
Male	7,278	536	7.4
50-65 years of age			
Female	6,412	370	5.8
Male	6,822	405	5.9
Nationality			
18-29 years of age			
other nationalities	10,884	2,563	23.5
Qatari	6,978	2,149	30.8
30-39 years of age			
other nationalities	18,082	2,164	12.0
Qatari	4,706	787	16.7
40-49 years of age			
other nationalities	12,815	1,032	8.1
Qatari	3,993	504	12.6
50-65 years of age			
other nationalities	9,377	518	5.5
Qatari	3,857	257	6.7
Season (year quarter)			
18-29 years of age			
First quarter	3,683	967	26.3
Second quarter	3,730	910	24.4
Third quarter	5,062	1,393	27.5
Fourth quarter	5,387	1,442	26.8
30-39 years of age			
First quarter	4,903	643	13.1
Second quarter	5,126	536	10.5
Third quarter	5,810	816	14.0
Fourth quarter	6,949	956	13.8
40-49 years of age			
First quarter	3,430	312	9.1
Second quarter	3,551	243	6.8
Third quarter	4,257	442	10.4
Fourth quarter	5,570	539	9.7
50-65 years of age			
First quarter	2,675	163	6.1
Second quarter	2,720	118	4.3
Third quarter	3,318	209	6.3
Fourth quarter	4,521	285	6.3
BMI Measurement in latest visit			

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	Total	Severe Vitamin D deficiency (<10 ng/ml)	
	N	N	%
18-29 years of age			
Acceptable (<25)	5,850	1,558	26.6
overweight (25-29.9)	3,912	982	25.1
grade 1 or low risk obesity (30-34.9)	2,193	587	26.8
grade 2 or moderate risk obesity (35-39.9)	1,016	316	31.1
obesity grade 3 (morbid obesity) (40+)	525	178	33.9
30-39 years of age			
Acceptable (<25)	3,826	443	11.6
overweight (25-29.9)	6,003	776	12.9
grade 1 or low risk obesity (30-34.9)	3,904	557	14.3
grade 2 or moderate risk obesity (35-39.9)	1,651	280	17.0
obesity grade 3 (morbid obesity) (40+)	785	162	20.6
40-49 years of age			
Acceptable (<25)	1,946	137	7.0
overweight (25-29.9)	4,239	346	8.2
grade 1 or low risk obesity (30-34.9)	3,191	340	10.7
grade 2 or moderate risk obesity (35-39.9)	1,339	141	10.5
obesity grade 3 (morbid obesity) (40+)	742	97	13.1
50-65 years of age			
Acceptable (<25)	1,457	53	3.6
overweight (25-29.9)	3,452	153	4.4
grade 1 or low risk obesity (30-34.9)	2,699	158	5.9
grade 2 or moderate risk obesity (35-39.9)	1,307	88	6.7
obesity grade 3 (morbid obesity) (40+)	704	51	7.2
Positive risk factor			
18-29 years of age			
None of the listed chronic diseases	14,738	3,922	26.6
Diabetes	1,716	431	25.1
Hypertension	575	133	23.1
Asthma	1,109	301	27.1
Stroke	7	2	28.6
Cardiovascular disease	47	7	14.9
Any of the listed chronic diseases	3,124	790	25.3
30-39 years of age			
None of the listed chronic diseases	16,333	2,161	13.2
Diabetes	4,093	535	13.1
Hypertension	2,135	217	10.2
Asthma	1,286	171	13.3
Stroke	18	2	11.1
Cardiovascular disease	101	12	11.9
Any of the listed chronic diseases	6,455	790	12.2
40-49 years of age			
None of the listed chronic diseases	9,166	905	9.9
Diabetes	4,608	390	8.5

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	Total	Severe Vitamin D deficiency (<10 ng/ml)	
	N	N	%
Hypertension	4,243	320	7.5
Asthma	1,241	108	8.7
Stroke	43	5	11.6
Cardiovascular disease	238	14	5.9
Any of the listed chronic diseases	7,642	631	8.3
50-65 years of age			
None of the listed chronic diseases	3,814	272	7.1
Diabetes	6,603	344	5.2
Hypertension	6,903	349	5.1
Asthma	1,441	61	4.2
Stroke	88	7	8.0
Cardiovascular disease	713	38	5.3
Any of the listed chronic diseases	9,420	503	5.3

Multivariate Discriminant Analysis was used to predict a severe vitamin D status based on age, nationality, gender, BMI and co-morbid chronic conditions. The multivariate modelling helps to control the confounding effect of all the explanatory variables included in the model.

As shown in **table 4**, age, gender and nationality were among the top three factors that predicts a severe form of vitamin D deficiency. An older age is associated with a decreased risk of having a severe deficiency status, similar to being a male. Whereas Qatari nationality is associated with a higher probability of having severe vitamin D deficiency. Although a higher BMI would be more predictive of severe deficiency, it occupied the bottom of the list of predictor variables. Among the chronic conditions included in the model, hypertension, cardiovascular diseases and stroke increased the risk of having severe vitamin D deficiency status. Whereas, diabetes and asthma were associated with a lower probability of having the outcome.

In addition, a model (formula) was provided to predict the risk of having severe vitamin D deficiency based on all the variables discussed previously. This formula can calculate the discriminant score called D. If D is less than -0.245 then the subject is considered at risk of having severe vitamin D deficiency. The more extreme the calculated D on the negative side the higher is the probability of having this severe form of vitamin D deficiency.

Table 4: Discriminant analysis with selected explanatory variables to predict subjects with severe vitamin D deficiency differentiating them from those with serum levels of 10+

	Variables ordered by absolute size of correlation (Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions) within function	Risk of having severe Vitamin D deficiency
Age in year	1	Decrease
Hypertension	2	Increase
Male Vs Female Gender	3	Decrease
Qatari Nationality Vs Others	4	Increase

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Diabetes	5	Decrease
Cardiovascular disease	6	Increase
Asthma	7	Decrease
Stroke	8	Increase
BMI Measurement	9	Increase
		Unstandardized coefficients
Gender (Male coded as one and females as zero)		0.310
Age in year		0.081
BMI Measurement in latest visit		-0.026
Nationality (Qatari coded as one and others as zero)		-0.531
Diabetes (coded as one when present and zero if absent)		0.022
Hypertension (coded as one when present and zero if absent)		-0.006
Asthma (coded as one when present and zero if absent)		0.154
Stroke (coded as one when present and zero if absent)		-0.345
Cardiovascular disease (coded as one when present and zero if absent)		-0.188
(Constant)		-2.296

D = -2.296 + [0.31 x (Gender)] + [0.081 x (Age in year)] + [-0.026 x (BMI Measurement in latest visit)] + [-0.531 x (Nationality)] + [0.022 x (Diabetes)] + [-0.006 x (Hypertension)] [0.154 x (Asthma)] + [-0.345 x (Stroke)] + [-0.188 x (Cardiovascular disease)].

Discriminant score (D) = -0.245. If D < -0.245 then the subject is expected to have severe vitamin D deficiency.

Discussion

This study explored the status of serum vitamin D among subjects seeking health care in the PHCC facilities. Using a very strict criteria for defining severe vitamin D deficiency (serum level <10 ng/ml), the prevalence rate was 14.1%. This rate is increased to 71.4% for the commonly defined deficiency status (serum level <20 ng/ml). Using a more lax criteria for defining vitamin D insufficiency would raise the prevalence rate to as high as 92.7%. Although the current study analyzed all the population, selection bias is expected to confound the interpretation of findings, since the doctors did serum testing for vitamin D on around a quarter of eligible population with no predefined criteria for ordering the test.

The high prevalence of vitamin D deficiency observed in the current study is comparable to that found in various subpopulations of Middle Eastern people as well as to that found in previous studies performed in Qatar. A systematic review of evidence in Qatar reported the weighted-average prevalence of vitamin D insufficiency of 90.4%[6]. Another systematic review found that severe vitamin D deficiency (<10 ng/ml) was most common in South Asia and the Middle East[22]. The prevalence of vitamin D deficiency in United Arab Emirates (UAE) was 85.4%[13]. In another study from Saudi Arabia conducted on adult males aged 20-74 years old, 87.8% had vitamin D level <20 ng/mL[10]. Similar reports of high prevalence of vitamin D deficiency and insufficiency status were also noticed for Jordanian and Moroccan women[11, 14].

Globally, vitamin D insufficiency is prevalent in all regions of the world[22]. In the United States of America (USA), the overall prevalence rate of vitamin D deficiency (≤20 ng/mL) was 41.6% among

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adults, with the higher rates in blacks (82.1%) and Hispanics (69.2%)[23]. The prevalence of vitamin D insufficiency in Qatar is comparable to that in nearby countries (Gulf and Middle East and North Africa "MENA" countries), while it is much higher than that in USA. A guideline for treating vitamin D deficiency is available in PHCC for pediatric age group, while it is missing for adults. This might explain the high prevalence of vitamin D insufficiency in PHCC population, which is similar to the less privileged population sectors of the USA. Other factors may also contribute in explaining differences between populations like skin pigmentation, type of clothing and amount of physical activity[24].

The current study showed a negative relation between the age of participants and the prevalence rate of vitamin D deficiency. The risk of deficiency status is declining with advancing age. Evidence supporting this finding was published in a study among UAE adults showing a positive trend for serum vitamin D level with advancing age[13]. Other studies supported the association between lower serum vitamin D concentration and younger age[14, 25, 26]. The explanation for this observation is the use of vitamin D supplementation for elderly people, especially women, who are getting used to taking multivitamin tablets. In addition, clothing habit/lifestyle modification among younger people could provide further explanations. Younger people prefer living in apartments and have less outdoor physical activity whereas older people prefer living in houses and have more outdoor physical activity when they were younger and also now[25]. Still many studies reported evidence for an opposite age association with vitamin D status. These studies reached to a conclusion that older age acts as a predictor for lower vitamin D level[10, 11, 22, 27, 28]. Possible explanation for this inverse association include: shortage in effective programs of prevention and treatment may results in vitamin D deficiency to be common among elderly[29]. A decreases in synthesis of vitamin D3 in the skin under influence of UV light with aging due to insufficient sunlight exposure, and a decreased functional capacity of the skin[30]. Aging is usually associated with a decrease in food intake, which may cause concurrent vitamin D deficiency[31].

In the current study, the severe form of vitamin D deficiency was more prevalent among females (almost double that of males). This gap would almost disappear when we compare both genders according to the insufficiency status. This finding agrees with a study from UAE reporting an almost similar mean serum vitamin D level for both genders[13]. In a Jordanian study conducted on subjects aged >18 years, the prevalence of low vitamin D status (<30 ng/mL) was 37.3% in females compared to only 5.1% in males. Dress style for females in Arabic culture was independently related to low vitamin D status; women wearing 'Hijab' (adjusted OR=1.7, p=0.004) or 'Niqab' (adjusted OR=1.5, p=0.061) were at a higher risk for low vitamin D status than were western-dressed women[27]. Other studies highlighted the higher risk of females for a deficiency status[22, 25, 32].

In the current study, Qatari nationality (local population) had the highest rate of severe deficiency (18.9%) compared to other nationalities (12.3%). The UAE study showed a statistically significant lower mean vitamin D level (19.1 ng/mL) among local people compared to non-locals (20.07 ng/mL)[13]. The type of dress covering the whole body (in females as well as males) may explain such a difference.

The current study reported the highest prevalence of severe vitamin D deficiency among obese individuals. In addition a positive trend for severe vitamin D deficiency was observed with increasing BMI. Many studies supported the fact that low serum vitamin D levels are significantly more common among obese people with BMI >30[10, 23, 32, 33]. Obesity-associated low vitamin D levels is possible due to the decreased bioavailability of vitamin D from cutaneous and dietary sources among obese people[9].

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Current study demonstrated that severe deficiency was less common among adults sampled during spring (second quarter), compared to other seasons. It seems that having a good weather during this time of the year in Qatar may invite sun exposure which stimulate production of vitamin D in the body. Saudi Arabia showed another type of seasonal variation where hypovitaminosis D was more common during spring and summer[10]. Another study from Morocco showed that vitamin D insufficiency was very common in healthy adult Moroccan women during summer[11].

In Europe, surprisingly vitamin D concentrations were higher in the Northern European and Scandinavian countries compared to Southern Europe. This could be partly explained by avoidance of sunlight exposure and inability to perform daily activities in Southern Europe compared to the Northern[31].

None of the five chronic conditions explored in the current study (diabetes, hypertension, asthma, stroke and cardiovascular disease) had an obvious association with severe vitamin D deficiency status in bivariate analysis. The multivariate modelling, however showed that (adjusting for age, gender, BMI and nationality and each of the included chronic conditions) hypertension, cardiovascular diseases and stroke increased the risk of having severe vitamin D deficiency status. Whereas, diabetes and asthma were associated with a lower probability of having the deficiency status.

There is an abundance of literature discussing the association between these chronic conditions and vitamin D status. Some suggested that vitamin D plays an important role in a broad range of organ functions, including cardiovascular health and thus a deficiency status would be associated with a significant increase in the prevalence of vascular disease, coronary artery disease, myocardial infarction, heart failure, and stroke[34]. This plausible explanation for a beneficial role of vitamin D in preventing or ameliorating the above listed conditions was consistently challenged by another group of literature failing to document a link between these conditions and vitamin D. In the following discussion we will try to present views from both parties.

Evidence in favor of a possible link between cardiovascular problems and low vitamin D status include the following. The prevalence of vitamin D insufficiency (<30 ng/mL) was higher in participants with selected cardiovascular disease risk factors, including obesity, hypertension, diabetes mellitus, hypertriglyceridemia and hypercholesterolemia[32, 35]. The results of a study from India found a significant correlation between the prevalence of vitamin D deficiency and acute coronary syndrome in comparison to healthy controls. In accordance to that study, vitamin D deficiency was associated with highly significant increase in the prevalence of peripheral vascular disease[36]. A study conducted on 239 patients with coronary artery disease revealed very high prevalence (up to 96%) of abnormally low vitamin D levels[37]. Severe vitamin D deficiency (<10 ng/mL) was shown to be independently associated with in-hospital cardiovascular mortality in 206 patients with acute coronary syndromes[38]. Severe vitamin D deficiency has been suggested to be strongly associated with sudden cardiac death, cardiovascular events and mortality and borderline associations with stroke and fatal infection[39]. In a cohort study conducted in USA, vitamin D deficiency was associated with an increased risk of all stroke cases (hemorrhagic and ischemic)[40].

Other studies failed to document a link between cardiovascular disease and vitamin D. In the study of Park S et al, serum vitamin D levels did not differ significantly between the cardiovascular disease and non-cardiovascular disease groups[41]. Similarly, the analysis carried in high-risk patients with stable

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coronary heart disease does not support a prognostic value of baseline-vitamin D levels for secondary cardiovascular event incidence or all-cause mortality[42].

Several studies assessed the association between serum levels of vitamin D and select cardiovascular disease risk factors in adults. Vitamin D level was significantly lower in hypertensives cases[23, 32, 35]. Vitamin D deficiency was associated with a significant increases in the prevalence of hypertension[34, 36]. Accumulating evidence derived from a systematic review favors the hypothesis that vitamin D deficiency contributes to arterial hypertension[43]. Two cohort studies monitored vitamin D levels for 4 to 8 years, these studies showed that the relative risk (adjusted by multivariate modelling) for incident hypertension for subjects with vitamin D deficiency (<15 ng/mL) was increased by six times in males and two times in females compared to those with a plasma level ≥30 ng/mL[44]. Increasing vitamin D level in the blood directly or indirectly has been shown to reduce blood pressure in several studies[45, 46]. Other studies failed to document a beneficial effect for vitamin D supplementation. A large prospective study by Forman et al. in 2005 found no association between vitamin D intake from diet or as supplements and the risk of incident hypertension[47]. In addition, several clinical trials using supplementation of vitamin D did not show any significant decrease in blood pressure[48-50].

Conflicting research evidence exits about the possible relation between vitamin D and diabetes mellitus. Some literature supported a positive association and suggested that hypovitaminosis D may be a significant risk factor for glucose intolerance in some, but not all, populations. Subjects with vitamin D deficiency status (<20 ng/mL) had a greater prevalence of components of metabolic syndromes including type 2 diabetes than did subjects with acceptable vitamin D status[51]. Type 2 diabetes patients had a higher incidence of hypovitaminosis D in different studies[23, 32, 52]. In addition, vitamin D deficiency was associated with a significant increase in prevalence and likelihood of developing of diabetes[34-36]. Two studies indicated that prolonged treatment of osteomalacia with vitamin D increases insulin secretion and improves glucose tolerance[53, 54]. Other literature failed to show a positive association or even showed an inverse association. Data from the Third National Health and Nutrition Examination Survey showed an inverse association between vitamin D status and diabetes in non-Hispanic white and Mexican American people, but not in non-Hispanic black people. An explanation for the lack of association could be the existence of a variable threshold effect among different ethnic groups[28]. In another study conducted on 1,071 randomly selected white English individuals aged 40 to 65 years, serum vitamin D levels were not related to glucose status[55].

Many studies were published about a possible role for vitamin D in childhood asthma. In adults, such an association was also subject to conflicting evidence. Among supporters for a possible positive association between asthma and low vitamin D is a study among African American showing that vitamin D deficiency was significantly greater among cases than controls (86% vs 19%)[56]. Conversely, another study showed that vitamin D deficiency was more frequent among healthy control compared to asthmatic cases[57]. In addition, two studies demonstrated that vitamin D supplementation increases the risk of allergic asthma[58, 59].

Conclusion

Although not comprehensive and nationally representative, this study is suggestive of a higher prevalence of vitamin D deficiency among young adults, females, Qatari nationality and those with higher BMI.

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No clear association was observed using bivariate analysis for any of the five chronic conditions explored in the current study with severe deficiency status. Multivariate modelling showed that hypertension, cardiovascular diseases and stroke increased the risk of having severe vitamin D deficiency status.

Recommendations

The high prevalence of vitamin D deficiency was based on a cut-off value of <20 ng/ml among adult population of PHC service users. Further evidence is required to justify the use of such a cut-off value or defining a new one more suitable for Qatar. In addition, an intervention study is needed to study the effectiveness of different treatment protocols in PHCC population.

Acknowledgments

We are extremely grateful to everyone who contributed to this work, especially the HIM team in PHCC.

Ethical approval

Appropriate approval was obtained from the PHCC Research Committee.

Funding

The PHCC Research Department in the State of Qatar funded the publication of this study.

Patient consent

No consents were needed as the data used in the study were anonymized.

Competing interest

None declared.

Figure legends

Figure 1: Among subjects with no evidence of prior vitamin D replacement therapy, the prevalence rate of the severe form of vitamin D deficiency (serum level <10 ng/ml) was 14.1% and this rate declined to 3.3% among treated individuals. On the other side, the prevalence rate of vitamin D deficiency (serum level <20 ng/ml) was 71.4% among non-treated subjects compared to 53.4% among treated ones. A third cut-off value for defining Vitamin D insufficiency is set at <30 ng/ml, at this level the prevalence rate was as high as 92.7% among the non-treated group reduced slightly to 87.8% among the treated group.

Data sharing statement

No additional data are available.

Contribution to authorship

AJZ and HAQ designed the study and wrote the primary proposal. AJZ managed data collection. MOS, HAQ and AJZ did the literature review. AHN and AJZ did data analysis, results interpretation and wrote the discussion. AJZ drafted the manuscript. HAQ, AHN and MOS revised the manuscript. AJZ finalized and submitted the manuscript.

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Acad Sci [Internet]. 2004 Dec [cited 2018 Nov 26];1037(1):84–95. Available from: http://doi.wiley.com/10.1196/annals.1337.013

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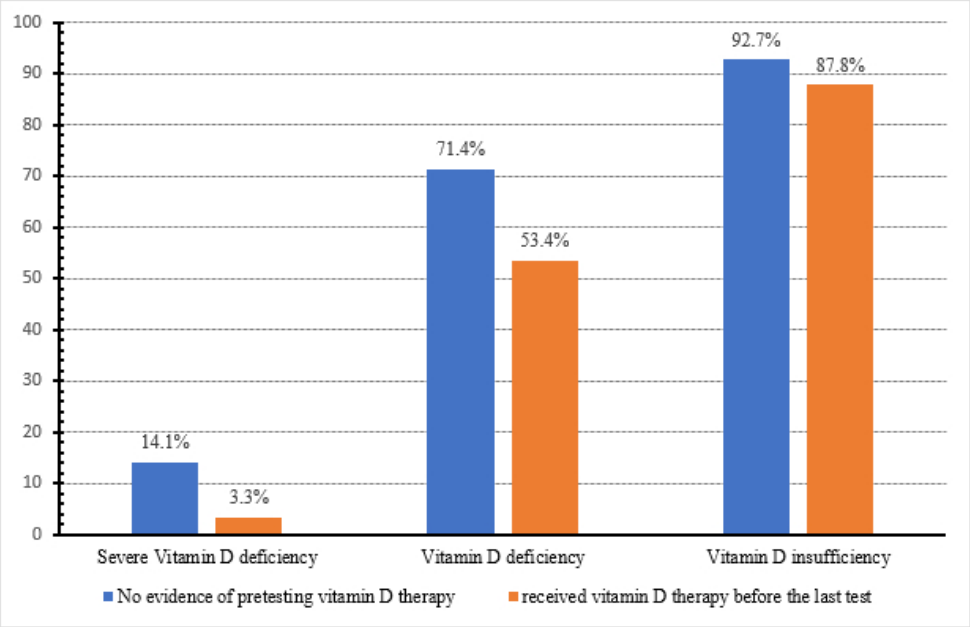

Figure 1: The prevalence rate of selected outcomes based on different serum Vitamin-D cut-off values among subjects with no evidence of Vitamin D therapy before testing compared to those who received such therapy

Among subjects with no evidence of prior vitamin D replacement therapy, the prevalence rate of the severe form of vitamin D deficiency (serum level <10 ng/ml) was 14.1% and this rate declined to 3.3% among treated individuals. On the other side, the prevalence rate of vitamin D deficiency (serum level <20 ng/ml) was 71.4% among non-treated subjects compared to 53.4% among treated ones. A third cut-off value for defining Vitamin D insufficiency is set at <30 ng/ml, at this level the prevalence rate was as high as 92.7% among the non-treated group reduced slightly to 87.8% among the treated group.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3, 4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	2
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5, 6
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	6, 7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-11

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		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	2
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Vitamin D status among adults (18-65 years old) attending Primary Health Care Centers in Qatar: A cross sectional analysis of the Electronic Medical Records for the year 2017

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029334.R1
Article Type:	Research
Date Submitted by the Author:	16-Jul-2019
Complete List of Authors:	Zainel, A.Jaleel; Primary Health Care Corporation, Clinical Affairs Qotba, Hamda; Primary Health Care Corporation, Clinical Affairs, Research Department Al Nuaimi , Ahmed ; Primary Health Care Corporation, Research Department, Clinical Affairs Directorate Syed , Mohamed; Primary Health Care Corporation, Research Department, Clinical Affairs Directorate
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Nutrition and metabolism, Evidence based practice
Keywords:	Vitamin D, Adults, Chronic disease, Prevalence, Qatar

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Vitamin D status among adults (18-65 years old) attending Primary Health Care Centers in Qatar: A cross sectional analysis of the Electronic Medical Records for the year 2017

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Abstract

Objectives To investigate the prevalence of vitamin D deficiency among individuals attending primary health care facilities in Qatar and to assess the association between vitamin D deficiency and some medical conditions in persons aged 18-65 years old.

Setting The study was undertaken in publicly funded primary health care services in the State of Qatar.

Participants A total of 102,342 participants aged between 18 and 65 years old with a valid serum vitamin D test result during the year 2017.

Outcome measures Serum level <10 ng/ml (<25 nmol/L) was defined as severe vitamin D deficiency, a serum level of <20 ng/ml (<50 nmol/L) was defined as vitamin D deficiency and a serum level <30 ng/ml (<75 nmol/L) defined as vitamin D insufficiency.

Results The prevalence rate of severe vitamin D deficiency was 14.1% among study participants with no history of vitamin D replacement therapy in the previous months. The prevalence rate of vitamin D deficiency was as high as 71.4% and that of vitamin D insufficiency was up to 92.7%. None of the five chronic conditions explored in the study (diabetes, hypertension, asthma, stroke and cardiovascular disease) had an obvious association with severe vitamin D deficiency status in a bivariate analysis. However, multivariate modelling showed that (adjusting for age, gender, body mass index and nationality and each of the included chronic conditions) hypertension, cardiovascular diseases and stroke placed an individual at a higher risk of having an associated severe Vitamin D deficiency status.

Conclusion Although not comprehensive and nationally representative, this study is suggestive of a higher prevalence of vitamin D deficiency among young adults, females, Qatari nationality and those with higher body mass index. Multivariate modelling showed that hypertension, cardiovascular diseases and stroke were associated with a higher risk of severe vitamin D deficiency status.

Key words: Vitamin D, Adults, Chronic disease, Prevalence, Qatar

Strengths and limitations of this Study

- An advantage of this study is that it used readily available data, which required fewer resources compared to collecting new data. The conclusions were therefore based on a very large set of data.
- The current cross-sectional study is not suitable to demonstrate temporality of any observed association. A longitudinal study design is needed to measure the risk of vitamin D deficiency for selected predisposing factors or determinants with confidence.
- Variability in the applied diagnostic criteria and laboratory cut-off values in identifying vitamin D deficiency and insufficiency across different studies may limit the ability of a fair comparison.
- Selection bias is an obvious limitation in this study. Physicians are expected to order serum Vitamin D test for specific service users according to special criteria and indications or personal preference, since no clear guideline are available for ordering the test. Therefore, not all people had equal chances to be included in this study.

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Introduction

Vitamin D is a steroid vitamin, which together with other physiological factors, controls the metabolism of calcium and phosphorus. There are different sources of vitamin D. Mainly exposure to the sun where ultraviolet B radiation promotes synthesis of vitamin D in the skin(1). Diet also plays a role on vitamin D status(2). The major dietary sources of vitamin D are milk, plant-based beverages, fortified fruit juices and yoghurts (3). Vitamin D deficiency can have serious consequences on health and is a widely spread micronutrient problem globally. Several risk factors are associated with low serum levels of vitamin D in adults. These include advancing age, female gender, clothing style, season, socio-economic status, urban living, dark skin and body mass index (BMI)(4, 5).

Vitamin D deficiency has been reported as a public health concern globally(6). While high prevalence of vitamin D deficiency has been reported globally, reliance on a single cut-off value to define vitamin D deficiency or insufficiency is problematic because of the wide individual variability of the functional effects of vitamin D and interaction with calcium intakes(6). In studies, cut-off values are often chosen when there is evidence of decreased risk for selected end-points for individuals with serum levels greater than that cut-off value. These end-points include fractures, cardiovascular diseases, colorectal cancer, diabetes, depressed mood, cognitive decline and death(7). Some published studies demonstrated vitamin D deficiency can be diagnosed when the level of serum vitamin D is <25 nmol/L (<10 ng/ml)(8). Others defined deficiency as serum vitamin D <50 nmol/L (<20 ng/ml)(7). The desirable level for an adult is > 75 nmol/L (>30 ng/ml). A U shape relation between serum vitamin D level and adverse outcome was noticed. A level of >250 nmol/L (>100 ng/ml) invites problems(8). A level of 20-30 ng/ml of serum vitamin D is known as insufficient or suboptimal vitamin D status(8).

Recently, vitamin D as a micronutrient and its deficiency has became more popular among the medical community as well as the public. Vitamin D deficiency in known to cause bone diseases in adults (9, 10). A study showed a positive correlation between bone mineral density values at both lumbar spine (L1-L4) and neck of femur and serum vitamin D levels, respectively(11). Apart from the well-established effect of vitamin D deficiency on diseases associated with bone growth, there is a wide array of other risk factors and medical conditions which in literature provide conflicting evidence of being associated with vitamin D deficiency.

A systematic review showed an increase in the prevalence of vitamin D deficiency with age(12). While a study conducted in Morocco, concluded that one of the main determinants of hypovitaminosis D was age > 55 years (13). While in a Saudi study, vitamin D deficiency was reported to be common among older men with no education and sedentary lifestyle (11). Joergensen and colleagues found that vitamin D level was not associated with gender(14). While a study conducted in Qatar reported that the mean overall vitamin D level was lower in females compared to males(15). This gender inequality was also reported by another study from the United Arab Emirates(16).

Vitamin D deficiency was found to be common among obese men with no education and sedentary lifestyle in a Saudi study(11). This observation was reported in another study on a group of healthy, white, obese medical school personnel, which showed that Body Mass Index (BMI) was inversely correlated with serum vitamin D3 concentrations(5). Clothing which covers all parts of the body, spending time outdoors for less than 30 minutes/day and urban living have shown negative effects on the level of serum vitamin D(13, 17). Spending more than one hour outdoors was independently associated with higher vitamin D levels(18).

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Evidence of other diseases and conditions, which may deteriorate or improve according to the level of serum vitamin D through an indirect mechanism are also available. Diabetes mellitus is more likely with vitamin D deficiency, as vitamin D acts through several mechanisms on glucose metabolism. Literature showed that Vitamin D can act on insulin producing cells (β cells) in the pancreas to produce more insulin, it acts on the muscle and fat cells to improve insulin action by reducing insulin resistance as well as vitamin D indirectly improves insulin production and its action by improving the level of calcium inside the cells(14, 19, 20, 21). In a study from Spain, vitamin D concentrations correlated negatively with total cholesterol and LDL cholesterol levels(18). Colorectal cancer mortality was inversely related to serum vitamin D level, with levels 80 nmol/L or higher associated with a 72% risk reduction compared with lower than 50 nmol/L(2). A cross-sectional study showed a positive correlation between bone mineral density values at both lumbar spine (L1-L4) and neck of femur and serum vitamin D levels, respectively(11).

In Qatar, prevalence of vitamin D deficiency has been reported as 90% (12, 15). The current study aims to investigate the prevalence of vitamin D deficiency among adult persons attending primary health care facilities in Qatar. In addition, it assessed the association between vitamin D deficiency and selected medical conditions (diabetes, asthma, hypertension, cardiovascular diseases, and stroke) in people aged 18-65 years old. The current study will test the hypothesis that these selected medical conditions are associated with vitamin D status to provide a much-needed snapshot of the extent of this micronutrient deficiency in the State of Qatar.

Methods

Study design: Cross-sectional study.

Study setting: Qatar, a peninsular Arab country with a high-income economy backed by the world's third-largest natural-gas reserves, has been investing significantly on its health care system. This includes a publicly funded primary health care (PHC) service delivered by the Primary Health Care Corporation (PHCC) which is the largest primary care provider publicly funded by the State of Qatar. At the time of undertaking this study, PHCC had 23 primary health care centers (all accredited by Accreditation Canada International) distributed across the country on three geographical regions. Every resident in Qatar with a valid residence permit is eligible to register with a PHCC health center for a nominal annual fee and utilize its services.

Study population: A total of 102,342 Electronic Medical Records (EMR) were extracted from PHCC's EMR system for service users aged between 18 and 65 years old with a valid serum vitamin D test result during the year 2017.

Study variables: The outcome variable was vitamin D deficiency which was tested at three cut-off values. The independent (exposure) variables included age, gender, nationality, BMI, and a list of selected chronic medical conditions. These included diabetes, hypertension, asthma, stroke and cardiovascular disease.

Data Collection: In PHCC, individuals are tested for vitamin D serum levels if requested by a doctor. The tests are conducted in health center laboratories. Blood drawn from an individual by a phlebotomist was processed using an Abbott ARCHETICT i1000SR IMMUNO analyzer designed to perform automated immunoassay tests, utilizing CMIA (chemiluminescent microparticle assay) detection technology. The results of the test were recorded by the laboratory on PHCC's EMR system. The laboratory internal quality control was conducted at the beginning of morning shift and judged by Westgard rules and Levey Jennings plot once daily. The external quality control followed the RIQAS (Randox International Quality

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Assessment Scheme) protocol. Data were extracted from the PHCC's EMR system for the defined study population. The data was extracted for a time period of one year starting from the 1st January to the 31st December 2017. A total of 421,283 adults (aged 18-65 years old) accessed primary healthcare services in 2017. Out of those active users, 102,342 individuals had a valid serum vitamin D measurement during the one-year study period. The PHCC EMR system uses SNOMED codes (a systematically organized computer processable collection of medical terms providing codes, terms, synonyms and definitions used in clinical documentation and reporting). These codes are quality controlled and reviewed by the Health Information Management (HIM) department of PHCC. The HIM department is responsible for translating SNOMED codes into ICD-10 codes (International Classification of Disease the tenth Revision) and continuously updating the coding manual with any new code used in the organizational database at a monthly interval. The HIM department provided a full list of variables for the study population using filters requested for the purpose of the study. The codes and algorithms used for specifying the data extraction process is described in Appendix A.

Data analysis: The Statistical Package for Social Sciences (IBM-SPSS Ver 23) was used for data analysis. Descriptive statistics were done first. Data cleaning involved logical checks for consistency of related variables (like being treated with Vitamin D replacement and the type of formulary used for treatment being valid for those treated only) and range checks for dates to be within the specified study time.

A review of the literature suggests many cut-off values for defining vitamin D inadequacy. For the purposes of this study, severe vitamin D deficiency was defined as having a serum level of <10 ng/ml, vitamin D deficiency was defined as having a serum level of <20 ng/ml and vitamin D insufficiency was defined as having a serum level of <30 ng/ml.

As treatment with replacement therapy was expected to affect the measured concentration of serum vitamin D, the extracted data was split into two groups. The individuals treated with vitamin D replacement therapy before the date label for testing serum concentration of vitamin D were included in the treatment group while the others in the untreated group.

Age was recoded into age groups of 10 years intervals. Only the first (18-29 years) and last (50-65 years) age groups were different in class interval width. BMI in Kg/m^2 was classified into 5 groups using the WHO classification. These groups were: Acceptable (<25), overweight (25-29.9), grade 1 or low risk obesity (30-34.9), grade 2 or moderate risk obesity (35-39.9) and obesity grade 3 (morbid obesity) (40+). The season during which testing of vitamin D took place was classified into quarters of a year (the first quarter for example included the months of January, February and March).

Multivariate discriminant analysis was used to predict a severe vitamin D status based on age, nationality, gender, BMI and co-morbid chronic conditions. The multivariate modelling helped to control the confounding effect of all the explanatory variables included in the model. No test of significance was needed since all the population with available data was analyzed and no attempt is made to generalize the conclusion to an untested population.

Quality control measures: In the preparation phase of the study, an extensive review of literature was undertaken and academic experts in community medicine and other related fields were consulted. The study authors were responsible for data collection in collaboration with the Health Information Management (HIM) department. Collection of blood and its laboratory analysis followed PHCC's standard operating procedures.

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Ethical Consideration: The study presented minimal risk of harm to its human participants. The data collected was anonymized. None of the study participants' personal information was revealed to the research team. Overall, the study was conducted with integrity according to generally accepted ethical principles and was approved by the PHCC's Research Committee.

Patient and Public Involvement: Patients' priorities, experience and preferences were not gathered nor were they involved in designing the study. PHCC's HIM department facilitated data collection. There are no plans to disseminate results to the study participants directly as they are already anonymized.

Results

The study results are based on the analysis of 102,342 primary health care service users (adults between 18 and 65 years old) with a valid serum vitamin D test result during the year 2017 as shown in **table 1**.

Table 1: Frequency distribution of the total study sample with an available recorded value for serum Vitamin D during the year 2017

	N	%
Age group in years		
18-29	23,348	22.8
30-39	30,889	30.2
40-49	24,736	24.2
50-65	23,369	22.8
Total	102,342	100.0
Gender		
Female	67,393	65.9
Male	34,946	34.1
Total	102,339	100.0
Nationality		
Other nationalities	72,314	70.7
Qatari	30,028	29.3
Total	102,342	100.0
Vitamin D therapy before the last serum Vitamin D test		
No	70,818	68.9
Yes	31,903	31.1
Total	102,721	100.0
BMI Measurement		
Acceptable (<25)	18,108	23.2
Overweight (25-29.9)	26,523	34.0
Grade 1 or low risk obesity (30-34.9)	19,549	25.1
Grade 2 or moderate risk obesity (35-39.9)	9,008	11.6
Grade 3 obesity (morbid obesity) (40+)	4,779	6.1
Total	77,967	100.0

Figure 1 demonstrates the prevalence rate of vitamin D insufficiency, deficiency and severe deficiency among treated and untreated study participants.

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As shown in **table 2**, the relation between sociodemographic factors and vitamin D status is relatively affected by the cut-off values of vitamin D. **Table 2** also shows there is no obvious or consistent seasonal variations in prevalence rate of vitamin D deficiency at any of the three tested cut-off values.

Table 2 shows age had a strong association with vitamin D deficiency status. In addition, age is known to be associated with BMI and other risk factors studied. Therefore, age qualifies as a strong confounder for any association between explanatory variables tested and the deficiency status. Undertaking a stratified analysis, adjusting for age as a confounder offers a solution to adjust for this undesired confounding effect.

Table 2: The prevalence of selected outcomes based on different serum vitamin D cut-off values for study participants with no evidence of vitamin D therapy before testing stratified by sociodemographic variables

	Total	Severe Vitamin D deficiency		Vitamin D deficiency		Vitamin D insufficiency	
	N	N	%	N	%	N	%
Age group in years							
18-29	17,862	4,712	26.4	14,610	81.8	17,036	95.4
30-39	22,788	2,951	12.9	16,565	72.7	21,276	93.4
40-49	16,808	1,536	9.1	11,482	68.3	15,522	92.3
50-65	13,234	775	5.9	7,847	59.3	11,711	88.5
Gender							
Female	44,773	7,459	16.7	32,649	72.9	41,328	92.3
Male	25,916	2,514	9.7	17,852	68.9	24,214	93.4
Nationality							
Other nationalities	51,158	6,277	12.3	36,344	71	47,905	93.6
Qatari	19,534	3,697	18.9	14,160	72.5	17,640	90.3
Season (year quarter) of testing for serum Vit D							
First quarter	14,691	2,085	14.2	10,697	72.8	13,753	93.6
Second quarter	15,127	1,807	11.9	10,682	70.6	14,092	93.2
Third quarter	18,447	2,860	15.5	13,545	73.4	17,183	93.1
Fourth quarter	22,427	3,222	14.4	15,580	69.5	20,517	91.5
BMI (Kg/m^2) Measurement in latest visit							
Acceptable (<25)	13,079	2,191	16.8	9,224	70.5	11,997	91.7
Overweight (25-29.9)	17,606	2,257	12.8	12,307	69.9	16,205	92.0
Grade 1 or low risk obesity (30-34.9)	11,987	1,642	13.7	8,676	72.4	11,134	92.9
Grade 2 or moderate risk obesity (35-39.9)	5,313	825	15.5	4,042	76.1	4,967	93.5
Grade 3 obesity (morbid obesity) (40+)	2,756	488	17.7	2,169	78.7	2,585	93.8

After adjusting for age group, the association between gender, nationality, season, BMI and selected chronic health conditions with the prevalence of severe vitamin D deficiency among individuals with no evidence of vitamin D therapy is shown in **table 3**.

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Table 3: The prevalence of severe vitamin D deficiency (<10 ng/ml) among study participants with no evidence of vitamin D replacement therapy before testing by selected explanatory variables after adjusting for age group

	Total	Severe Vitamin D deficiency (<10 ng/ml)	
	N	N	%
Gender			
18-29 years of age			
Female	13,712	3,900	28.4
Male	4,150	812	19.6
30-39 years of age			
Female	15,121	2,190	14.5
Male	7,666	761	9.9
40-49 years of age			
Female	9,528	999	10.5
Male	7,278	536	7.4
50-65 years of age			
Female	6,412	370	5.8
Male	6,822	405	5.9
Nationality			
18-29 years of age			
Other nationalities	10,884	2,563	23.5
Qatari	6,978	2,149	30.8
30-39 years of age			
Other nationalities	18,082	2,164	12.0
Qatari	4,706	787	16.7
40-49 years of age			
Other nationalities	12,815	1,032	8.1
Qatari	3,993	504	12.6
50-65 years of age			
Other nationalities	9,377	518	5.5
Qatari	3,857	257	6.7
Season (year quarter)			
18-29 years of age			
First quarter	3,683	967	26.3
Second quarter	3,730	910	24.4
Third quarter	5,062	1,393	27.5
Fourth quarter	5,387	1,442	26.8
30-39 years of age			
First quarter	4,903	643	13.1
Second quarter	5,126	536	10.5
Third quarter	5,810	816	14.0
Fourth quarter	6,949	956	13.8
40-49 years of age			
First quarter	3,430	312	9.1
Second quarter	3,551	243	6.8
Third quarter	4,257	442	10.4

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	Total	Severe Vitamin D deficiency (<10 ng/ml)	
	N	N	%
Fourth quarter	5,570	539	9.7
50-65 years of age			
First quarter	2,675	163	6.1
Second quarter	2,720	118	4.3
Third quarter	3,318	209	6.3
Fourth quarter	4,521	285	6.3
BMI Measurement in latest visit			
18-29 years of age			
Acceptable (<25)	5,850	1,558	26.6
Overweight (25-29.9)	3,912	982	25.1
Grade 1 or low risk obesity (30-34.9)	2,193	587	26.8
Grade 2 or moderate risk obesity (35-39.9)	1,016	316	31.1
Obesity grade 3 (morbid obesity) (40+)	525	178	33.9
30-39 years of age			
Acceptable (<25)	3,826	443	11.6
Overweight (25-29.9)	6,003	776	12.9
Grade 1 or low risk obesity (30-34.9)	3,904	557	14.3
Grade 2 or moderate risk obesity (35-39.9)	1,651	280	17.0
Obesity grade 3 (morbid obesity) (40+)	785	162	20.6
40-49 years of age			
Acceptable (<25)	1,946	137	7.0
Overweight (25-29.9)	4,239	346	8.2
Grade 1 or low risk obesity (30-34.9)	3,191	340	10.7
Grade 2 or moderate risk obesity (35-39.9)	1,339	141	10.5
Obesity grade 3 (morbid obesity) (40+)	742	97	13.1
50-65 years of age			
Acceptable (<25)	1,457	53	3.6
Overweight (25-29.9)	3,452	153	4.4
Grade 1 or low risk obesity (30-34.9)	2,699	158	5.9
Grade 2 or moderate risk obesity (35-39.9)	1,307	88	6.7
Obesity grade 3 (morbid obesity) (40+)	704	51	7.2
Positive risk factor			
18-29 years of age			
None of the listed chronic diseases	14,738	3,922	26.6
Diabetes	1,716	431	25.1
Hypertension	575	133	23.1
Asthma	1,109	301	27.1
Stroke	7	2	28.6
Cardiovascular disease	47	7	14.9
Any of the listed chronic diseases	3,124	790	25.3
30-39 years of age			
None of the listed chronic diseases	16,333	2,161	13.2
Diabetes	4,093	535	13.1
Hypertension	2,135	217	10.2

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	Total	Severe Vitamin D deficiency (<10 ng/ml)	
	N	N	%
Asthma	1,286	171	13.3
Stroke	18	2	11.1
Cardiovascular disease	101	12	11.9
Any of the listed chronic diseases	6,455	790	12.2
40-49 years of age			
None of the listed chronic diseases	9,166	905	9.9
Diabetes	4,608	390	8.5
Hypertension	4,243	320	7.5
Asthma	1,241	108	8.7
Stroke	43	5	11.6
Cardiovascular disease	238	14	5.9
Any of the listed chronic diseases	7,642	631	8.3
50-65 years of age			
None of the listed chronic diseases	3,814	272	7.1
Diabetes	6,603	344	5.2
Hypertension	6,903	349	5.1
Asthma	1,441	61	4.2
Stroke	88	7	8.0
Cardiovascular disease	713	38	5.3
Any of the listed chronic diseases	9,420	503	5.3

Multivariate discriminant analysis was used to predict a severe vitamin D status based on age, nationality, gender, BMI and co-morbid chronic conditions. As shown in **table 4**, age, gender and nationality were among the top three factors that predicts a severe form of vitamin D deficiency. An older age is associated with a decreased risk of having a severe deficiency status, like the effect of being a male. Whereas Qatari nationality is associated with a higher probability of having severe vitamin D deficiency. Although a higher BMI would be more predictive of severe deficiency, it was at the bottom of the list of predictor variables. Among the chronic conditions included in the model, hypertension, cardiovascular diseases and stroke increased the risk of having an associated severe vitamin D deficiency status. While, diabetes and asthma were associated with a lower probability of having the outcome.

In addition, a model (formula) was provided to predict the risk of having an associated severe vitamin D deficiency based on all the variables discussed previously. The formula can calculate the discriminant score "D". If D is less than -0.245 then the individual is considered at risk of having severe vitamin D deficiency. The more extreme the calculated D on the negative side the higher is the probability for the individual to have this severe form of vitamin D deficiency.

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Table 4: Discriminant analysis with selected explanatory variables to predict study participants with severe vitamin D deficiency differentiating them from those with serum levels of 10+

	Variables ordered by absolute size of correlation (Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions) within function	Risk of having severe Vitamin D deficiency
Age in year	1	Decrease
Hypertension	2	Increase
Male Vs Female Gender	3	Decrease
Qatari Nationality Vs Others	4	Increase
Diabetes	5	Decrease
Cardiovascular disease	6	Increase
Asthma	7	Decrease
Stroke	8	Increase
BMI Measurement	9	Increase
		Unstandardized coefficients
Gender (Male coded as one and females as zero)		0.310
Age in year		0.081
BMI Measurement in latest visit		-0.026
Nationality (Qatari coded as one and others as zero)		-0.531
Diabetes (coded as one when present and zero if absent)		0.022
Hypertension (coded as one when present and zero if absent)		-0.006
Asthma (coded as one when present and zero if absent)		0.154
Stroke (coded as one when present and zero if absent)		-0.345
Cardiovascular disease (coded as one when present and zero if absent)		-0.188
(Constant)		-2.296

D = -2.296 + [0.31 x (Gender)] + [0.081 x (Age in year)] + [-0.026 x (BMI Measurement in latest visit)] + [-0.531 x (Nationality)] + [0.022 x (Diabetes)] + [-0.006 x (Hypertension)] [0.154 x (Asthma)] + [-0.345 x (Stroke)] + [-0.188 x (Cardiovascular disease)].

Discriminant score (D) = -0.245. If D < -0.245 then the individual is expected to have severe vitamin D deficiency.

Discussion

This study explored the status of serum vitamin D among individuals accessing PHCC health care centers in Qatar. Using strict criteria for defining severe vitamin D deficiency (serum level <10 ng/ml), the prevalence rate was 14.1%. This rate is increased to 71.4% for the commonly defined deficiency status (serum level <20 ng/ml). Using laxer criteria for defining vitamin D insufficiency would raise the prevalence rate to as high as 92.7%. Although the current study analyzed all the population, selection bias is expected to confound the interpretation of findings as vitamin D serum testing was only done on a quarter of eligible population. No guideline or protocol was used to identify the eligible population.

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The high prevalence of vitamin D deficiency observed in the current study is comparable to that found in various subpopulations of the Middle Eastern as well as to that found in previous studies performed in Qatar. A systematic review of evidence in Qatar reported the weighted-average prevalence of vitamin D insufficiency of 90.4%(12). Another systematic review found that severe vitamin D deficiency (<10 ng/ml) was most common in South Asia and the Middle East(22). The prevalence of vitamin D deficiency in United Arab Emirates (UAE) was 85.4%(16). In another study from Saudi Arabia conducted on adult males aged 20-74 years old, 87.8% had vitamin D level <20 ng/mL(11). Similar reports of high prevalence of vitamin D deficiency and insufficiency status were also reported for Jordanian and Moroccan women(13, 17).

Globally, vitamin D insufficiency is prevalent in all regions of the world(22). In the United States of America (USA), the overall prevalence rate of vitamin D deficiency (≤20 ng/mL) was 41.6% among adults, with the higher rates in blacks (82.1%) and Hispanics (69.2%)(23). The prevalence of vitamin D insufficiency in Qatar is comparable to that in nearby countries (Gulf and Middle East and North Africa "MENA" countries), while it was much higher than that in USA. A guideline for treating vitamin D deficiency is available in PHCC for pediatric age group, however, one for adults is yet to be developed. This might explain the high prevalence of vitamin D insufficiency in PHCC population, which is like the less privileged population sectors of the USA. Other factors may also contribute in explaining differences between populations like skin pigmentation, type of clothing and amount of physical activity(24).

The current study showed a negative relation between the age of participants and the prevalence rate of vitamin D deficiency. The risk of deficiency status is declining with advancing age. Evidence supporting this finding was published in a study among UAE adults showing a positive trend for serum vitamin D level with advancing age(16). Other studies supported the association between lower serum vitamin D concentration and younger age(17, 25, 26). The explanation for this observation is the use of vitamin D supplementation for elderly people, especially women, who are getting used to taking multivitamin tablets. In addition, clothing habit/lifestyle modification among younger people could provide further explanations. Younger people prefer living in apartments and have less outdoor physical activity whereas older people prefer living in houses and have more outdoor physical activity when they were younger and also now(25). Still many studies reported evidence for an opposite age association with vitamin D status. These studies reached to a conclusion that older age acts as a predictor for lower vitamin D level(11, 13, 22, 27, 28). Possible explanation for this include shortage in effective programs of prevention and treatment may results in vitamin D deficiency to be common among elderly(29). A decreases in synthesis of vitamin D3 in the skin under influence of UV light with aging due to insufficient sunlight exposure, and a decreased functional capacity of the skin(30). Aging is usually associated with a decrease in food intake, which may cause concurrent vitamin D deficiency(31).

In the current study, the severe form of vitamin D deficiency was more prevalent among females (almost double that of males). This gap would almost disappear when we compare both genders according to the insufficiency status. This finding agrees with a study from UAE reporting an almost similar mean serum vitamin D level for both genders(16). In a Jordanian study conducted on study participants aged >18 years, the prevalence of low vitamin D status (<30 ng/mL) was 37.3% in females compared to only 5.1% in males. Dress style for females in Arabic culture was independently related to low vitamin D status; women wearing 'Hijab' (adjusted OR=1.7, p=0.004) or 'Niqab' (adjusted OR=1.5, p=0.061) were at a higher risk for low vitamin D status than were western-dressed women(27). Other studies highlighted the higher risk of females for a deficiency status(22, 25, 32).

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In the current study, Qatari nationality (local population) had the highest rate of severe deficiency (18.9%) compared to other nationalities (12.3%). The UAE study showed a statistically significant lower mean vitamin D level (19.1 ng/mL) among the local population compared to expatriates (20.07 ng/mL)(16). The type of dress covering the whole body (in females as well as males) may explain such a difference.

Our study reports highest prevalence of severe vitamin D deficiency among obese individuals. In addition a positive trend for severe vitamin D deficiency was observed with increasing BMI. Many studies supported the fact that low serum vitamin D levels are significantly more common among obese people with BMI >30(11, 23, 32, 33). Obesity-associated low vitamin D levels is possible due to the decreased bioavailability of vitamin D from cutaneous and dietary sources among obese people(5).

Current study demonstrated that severe deficiency was less common among adults sampled during spring (second quarter), compared to other seasons. It seems that having good weather during this time of the year in Qatar may allow sun exposure which stimulate production of vitamin D in the body. Saudi Arabia showed that hypovitaminosis D was more common during spring and summer(11). Another study from Morocco showed that vitamin D insufficiency was very common in healthy adult Moroccan women during summer(13). In Europe, surprisingly vitamin D concentrations were higher in the Northern European and Scandinavian countries compared to Southern Europe. This could be partly explained by avoidance of sunlight exposure and inability to perform daily activities in Southern Europe compared to the Northern(31).

None of the five chronic conditions explored in the current study (diabetes, hypertension, asthma, stroke and cardiovascular disease) had an obvious association with severe vitamin D deficiency status in bivariate analysis. The multivariate modelling, however showed that (adjusting for age, gender, BMI and nationality and each of the included chronic conditions) hypertension, cardiovascular diseases and stroke increased the risk of having an associated severe vitamin D deficiency status. Whereas, diabetes and asthma were associated with a lower probability of having an associated deficiency status. There is an abundance of literature discussing the association between these chronic conditions and vitamin D status. Some suggested that vitamin D plays an important role in a broad range of organ functions, including cardiovascular health and thus a deficiency status would be associated with a significant increase in the prevalence of vascular disease, coronary artery disease, myocardial infarction, heart failure, and stroke(34). This plausible explanation for a beneficial role of vitamin D in preventing or ameliorating the above listed conditions was consistently challenged by another group of literature failing to document a link between these conditions and vitamin D.

Evidence in favor of a possible link between cardiovascular problems and low vitamin D status has been reported in studies. The prevalence of vitamin D insufficiency (<30 ng/mL) was higher in participants with selected cardiovascular disease risk factors, including obesity, hypertension, diabetes mellitus, hypertriglyceridemia and hypercholesterolemia(32, 35). The results of a study from India found a significant correlation between the prevalence of vitamin D deficiency and acute coronary syndrome in comparison to healthy controls. In accordance to that study, vitamin D deficiency was associated with a statistically significant increase in the prevalence of peripheral vascular disease(36). A study conducted on 239 patients with coronary artery disease revealed very high prevalence (up to 96%) of abnormally low vitamin D levels(37). Severe vitamin D deficiency (<10 ng/mL) was shown to be independently associated with in-hospital cardiovascular mortality in 206 patients with acute coronary syndromes(38). Severe vitamin D deficiency has been suggested to be strongly associated with sudden cardiac death, cardiovascular events and mortality and borderline associated with stroke and fatal infection(39). In a cohort

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study conducted in USA, vitamin D deficiency was associated with an increased risk of all stroke cases (hemorrhagic and ischemic)(40). Other studies failed to document a link between cardiovascular disease and vitamin D. In the study by Park et al, serum vitamin D levels did not differ significantly between the cardiovascular disease and non-cardiovascular disease groups(41). Similarly, the analysis carried in high-risk patients with stable coronary heart disease does not support a prognostic value of baseline-vitamin D levels for secondary cardiovascular event incidence or all-cause mortality(42).

Several studies assessed the association between serum levels of vitamin D and select cardiovascular disease risk factors in adults. Vitamin D level was significantly lower in hypertensives cases(23, 32, 35). In addition, Vitamin D deficiency was associated with a significant increases in the prevalence of hypertension(34, 36). Accumulating evidence derived from a systematic review favors the hypothesis that vitamin D deficiency contributes to arterial hypertension(43). Two cohort studies monitored vitamin D levels for 4 to 8 years, these studies showed that the relative risk (adjusted by multivariate modelling) for incident hypertension for individuals with vitamin D deficiency (<15 ng/mL) was increased by six times in males and two times in females compared to those with a plasma level ≥30 ng/mL(44). Increasing vitamin D level in the blood has been directly or indirectly shown to reduce blood pressure in several studies(45, 46). Other studies failed to document a beneficial effect for vitamin D supplementation. A large prospective study by Forman et al in 2005 found no association between vitamin D intake from diet or as supplements and the risk of incident hypertension(47). In addition, several clinical trials using supplementation of vitamin D did not show any significant decrease in blood pressure(48, 49, 50).

Conflicting research evidence exits about the possible relation between vitamin D and diabetes mellitus. Some literature supported a positive association and suggested that hypovitaminosis D may be a significant risk factor for glucose intolerance in some, but not all, populations. Individuals with vitamin D deficiency status (<20 ng/mL) had a greater prevalence of components of metabolic syndromes including type 2 diabetes than did those with acceptable vitamin D status(51). Type 2 diabetes patients had a higher incidence of hypovitaminosis D in different studies(23, 32, 52). In addition, vitamin D deficiency was associated with a significant increase in prevalence and likelihood of developing of diabetes(34, 35, 36). Two studies indicated that prolonged treatment of osteomalacia with vitamin D increases insulin secretion and improves glucose tolerance(53, 54). Other literature failed to show a positive association or even showed an inverse association. Data from the Third National Health and Nutrition Examination Survey showed an inverse association between vitamin D status and diabetes in non-Hispanic white and Mexican American people, but not in non-Hispanic black people. An explanation for the lack of association could be the existence of a variable threshold effect among different ethnic groups(28). In another study conducted on 1,071 randomly selected white English individuals aged 40 to 65 years, serum vitamin D levels were not related to glucose status(55).

Many studies were published about a possible role for vitamin D in childhood asthma. In adults, such an association was also subject to conflicting evidence. Among supporters for a possible positive association between asthma and low vitamin D is a study among African American showing that vitamin D deficiency was significantly greater among cases than controls (86% vs 19%)(56). Conversely, another study showed that vitamin D deficiency was more frequent among healthy control compared to asthmatic cases(57). In addition, two studies demonstrated that vitamin D supplementation increases the risk of allergic asthma(58, 59).

The current study is subject to well-known sources of bias, which needs to be addressed as limitations. The study used an analytical cross-sectional design, therefore any reported associations between selected

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explanatory variables and vitamin D status or absence of such explored associations should not be interpreted in the sense of risk or predictors. Since temporality as a criteria of causality cannot be verified in a cross-sectional design. One is unable to decide whether vitamin D deficiency status resulted in a specific disease status or that status was the precipitating factor for the deficiency status. Only age, gender and to some extent nationality are expected to be incriminated as risk factors, since these are fixed criteria. In addition, difference in the applied diagnostic criteria and laboratory cut-off values in identifying vitamin D deficiency and insufficiency across different studies may limit the ability of a fair comparison between studies. Selection bias is always a limitation in observational designs. Although the whole population satisfying the inclusion criteria was analyzed in the current study, they still represent a selected group of approximately one fourth of the total population seeking primary health care services during the one year study period. This part of the population who had their vitamin D serum tested was not a randomly selected subgroup, since the physicians requesting this biochemical test would have used some special criteria and indications to order the test, which is not standardized to follow a clinical guideline. Therefore, not all people had equal chances to be included in this study and the results cannot be generalized to every adult seeking health services in primary care setting. Based on the preceding argument the researcher is inclined to expect the reported results for vitamin D deficiency to represent a slight overestimate of the real situation.

Conclusion

Although not comprehensive and nationally representative, this study is suggestive of a higher prevalence of vitamin D deficiency among young adults, females, Qatari nationality and those with higher BMI. No clear association was observed using bivariate analysis for any of the five chronic conditions explored in the current study with severe deficiency status. Multivariate modelling showed that hypertension, cardiovascular diseases and stroke increased the risk of having an associated severe vitamin D deficiency status.

Recommendations

The high prevalence of vitamin D deficiency was based on a cut-off value of <20 ng/ml among adult population of PHC service users. Further evidence is required to justify the use of such a cut-off value or defining a new cut-off value that is more suitable for Qatar. In addition, an intervention study is needed to study the effectiveness of different treatment protocols in PHCC population.

Acknowledgments

We are extremely grateful to everyone who contributed to this work, especially the HIM department in PHCC.

Ethical approval

Appropriate approval was obtained from the PHCC Research Committee.

Funding

No funding was requested or received for the current study.

Patient consent

No consents from human participants were needed as the study used anonymized data obtained from PHCC official Electronic Medical Record system.

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Competing interest

None declared.

Figure legends

Figure 1: Among study participants with no evidence of prior vitamin D replacement therapy, the prevalence rate of the severe form of vitamin D deficiency (serum level <10 ng/ml) was 14.1% and this rate declined to 3.3% among treated individuals. On the other side, the prevalence rate of vitamin D deficiency (serum level <20 ng/ml) was 71.4% among non-treated study participants compared to 53.4% among treated ones. A third cut-off value for defining Vitamin D insufficiency is set at <30 ng/ml, at this level the prevalence rate was as high as 92.7% among the non-treated group reduced slightly to 87.8% among the treated group.

Data sharing statement

No additional data are available.

Contribution to authorship

AJZ and HAQ designed the study and wrote the primary proposal. AJZ managed data collection. MAS, HAQ and AJZ did the literature review. AHN and AJZ did data analysis, results interpretation and wrote the discussion. AJZ drafted the manuscript. HAQ, AHN and MOS revised the manuscript. AJZ finalized and submitted the manuscript. AHN and MAS replied to reviewers comments and amended the manuscript accordingly

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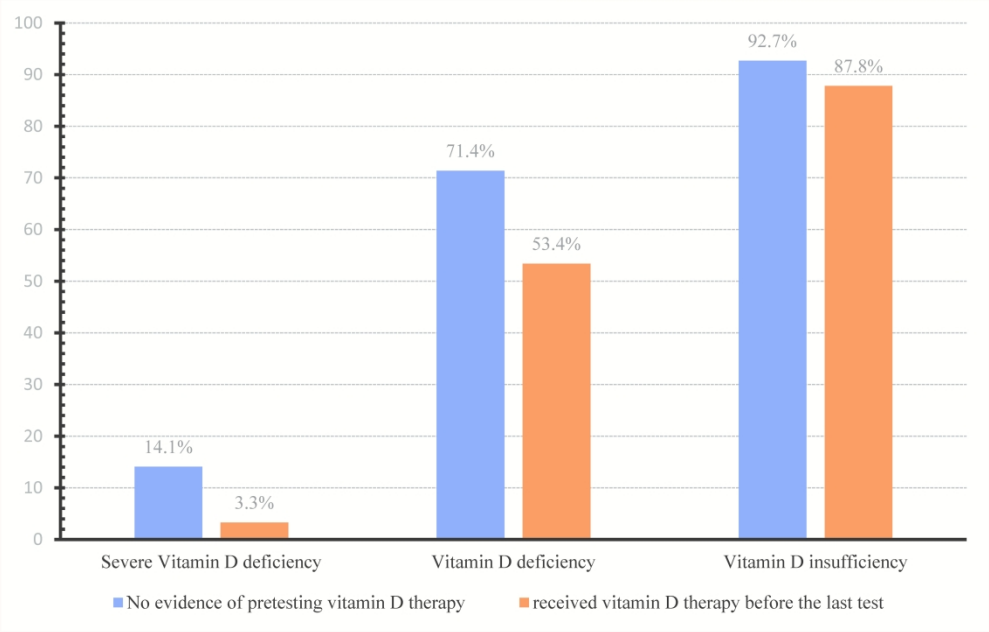

The prevalence rate of selected outcomes based on different serum Vitamin D cut-off values among individuals with no evidence of Vitamin D replacement therapy before testing compared to those who received such therapy

157x101mm (600 x 600 DPI)

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List of study variables extracted

The diagnosis of diabetes mellitus, hypertension and Asthma was available in two forms. The consolidated diagnosis, which represents the reason for the current medical encounter documented by the physician and the problem list diagnosis, which represents the list of chronic diseases for the patient disregarding the reason for current medical encounter (visit). The final variable used in the analysis would represent a positive status for any of the two forms of positive disease labels (consolidated diagnosis and/or problem list diagnosis).

Variable name	**Description**
DX_DIABETES	Consolidate Diagnosis of Diabetes Mellitus Documented by Physician in any visit
DX_HYPERTENSION	Consolidate Diagnosis of Hypertension Documented by Physician in any visit
DX_ASTHMA	Consolidate Diagnosis of Asthma Documented by Physician in any visit
P_DIABETES	Diabetes Mellitus recorded in Problem List
P_HYPERTENSION	Hypertension recorded in Problem List
P_ASTHMA	Asthma recorded in Problem List

The diagnosis of stroke and other cardiovascular diseases is only available in consolidated diagnosis form.

Variable name	**Description**
DX_STROKE	Consolidate Diagnosis of Stroke Documented by Physician in any visit
DX_OTHER_CVD	Consolidate Diagnosis of Cardiovascular disease Documented by Physician in any visit

Other variables included in the database include (in addition to age, gender and nationality):

Variable name	Description
VITD_LAST	Serum Vitamin D concentration (ng/ml)
VITD_LAST_DT_TM	Serum Vitamin D measurement date
Medication	Formulary type of Vitamin D replacement therapy
FIRST_ORDER_DATE	Date of Vitamin D replacement therapy prescription
BMI_MEASURE	BMI Measurement in latest visit
BMI_MEASURE_DT	BMI Measurement date

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The list of SNOMED and ICD-10 translation codes used to define selected health conditions

Stroke

SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
1217630014	SAH - Subarachnoid hemorrhage	I60.9	Subarachnoid haemorrhage, unspecified
2819960017	Intracerebral hemorrhage (ICH)	I61.9	Intracerebral haemorrhage, unspecified
2770034014	Cerebral infarction	I63.9	Cerebral infarction, unspecified
300370010	Left sided CVA	I64	Stroke, not specified as haemorrhage or infarction
300371014	Right sided CVA	I64	Stroke, not specified as haemorrhage or infarction
345635016	CVA - Cerebrovascular accident	I64	Stroke, not specified as haemorrhage or infarction
345636015	Stroke	I64	Stroke, not specified as haemorrhage or infarction
345642016	Total anterior cerebral circulation stroke	I64	Stroke, not specified as haemorrhage or infarction
345647010	Partial anterior cerebral circulation stroke	I64	Stroke, not specified as haemorrhage or infarction
1209750017	Thrombotic stroke	I64	Stroke, not specified as haemorrhage or infarction
2644233012	Ischemic stroke	I64	Stroke, not specified as haemorrhage or infarction
92070010	Cerebral atherosclerosis	I67.2	Cerebral atherosclerosis
427283015	Cerebral ischemia	I67.8	Other specified cerebrovascular diseases
104563015	Cerebrovascular disease	I67.9	Cerebrovascular disease, unspecified
300366019	Cerebellar stroke syndrome	I67.9	Cerebrovascular disease, unspecified
499414018	CVD - Cerebrovascular disease	I67.9	Cerebrovascular disease, unspecified
300411016	Sequelae of cerebral infarction	I69.3	Sequelae of cerebral infarction
300404015	Sequelae of cerebrovascular disease	I69.8	Sequelae of other and unspecified cerebrovascular diseases

Cardiovascular diseases

SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
7845011	Unstable angina	I20.0	Unstable angina
1488382011	Acute coronary syndrome	I20.0	Unstable angina
2579561010	ACS - Acute coronary syndrome	I20.0	Unstable angina
2819370013	Preinfarction angina	I20.0	Unstable angina
350348018	Stable angina	I20.8	Other forms of angina pectoris
442204010	Angina on effort	I20.8	Other forms of angina pectoris
1210402019	Atypical angina	I20.8	Other forms of angina pectoris

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
299755016	Angina	I20.9	Angina pectoris, unspecified
442205011	Exertional angina	I20.9	Angina pectoris, unspecified
498328016	Angina at rest	I20.9	Angina pectoris, unspecified
104192010	Acute anteroseptal myocardial infarction	I21.0	Acute transmural myocardial infarction of anterior wall
1231324017	Acute anterior myocardial infarction	I21.0	Acute transmural myocardial infarction of anterior wall
1233238016	Acute anterolateral myocardial infarction	I21.0	Acute transmural myocardial infarction of anterior wall
1233665015	Acute inferior myocardial infarction	I21.1	Acute transmural myocardial infarction of inferior wall
1787486017	NSTEMI - Non-ST segment elevation MI	I21.4	Acute subendocardial myocardial infarction
37436014	Myocardial infarction	I21.9	Acute myocardial infarction, unspecified
37441018	Infarction of heart	I21.9	Acute myocardial infarction, unspecified
94884017	Acute myocardial infarction	I21.9	Acute myocardial infarction, unspecified
1784872019	MI - Myocardial infarction	I21.9	Acute myocardial infarction, unspecified
1784873012	Myocardial infarct	I21.9	Acute myocardial infarction, unspecified
2534667013	Acute ischemic heart disease	I24.9	Acute ischaemic heart disease, unspecified
2534669011	Acute myocardial ischemia	I24.9	Acute ischaemic heart disease, unspecified
459859010	Asymptomatic coronary heart disease	I25.1	Atherosclerotic heart disease
89331010	Coronary arteriosclerosis	I25.10	Atherosclerotic heart disease, of unspecified vessel
89332015	Atherosclerotic heart disease	I25.10	Atherosclerotic heart disease, of unspecified vessel
2535923015	Triple vessel coronary artery disease	I25.10	Atherosclerotic heart disease, of unspecified vessel
2536392019	ASHD - Atherosclerotic heart disease	I25.10	Atherosclerotic heart disease, of unspecified vessel
2536393012	Arteriosclerotic heart disease	I25.10	Atherosclerotic heart disease, of unspecified vessel
2536397013	CHD - Coronary heart disease	I25.10	Atherosclerotic heart disease, of unspecified vessel
2536398015	Coronary heart disease	I25.10	Atherosclerotic heart disease, of unspecified vessel
2536394018	CAD - Coronary artery disease	I25.11	Atherosclerotic heart disease, of native coronary artery
2536395017	Coronary artery disease	I25.11	Atherosclerotic heart disease, of native coronary artery
299794015	Ischemic cardiomyopathy	I25.5	Ischaemic cardiomyopathy

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
2537483013	Chronic coronary insufficiency	I25.8	Other forms of chronic ischaemic heart disease
299761018	Ischemic heart disease - angina	I25.9	Chronic ischaemic heart disease, unspecified
395785017	Transient cerebral ischemia	I25.9	Chronic ischaemic heart disease, unspecified
2534663012	Ischemic heart disease	I25.9	Chronic ischaemic heart disease, unspecified
2534671011	Chronic ischemic heart disease	I25.9	Chronic ischaemic heart disease, unspecified
2534673014	Chronic myocardial ischemia	I25.9	Chronic ischaemic heart disease, unspecified
2537479013	IHD - Ischemic heart disease	I25.9	Chronic ischaemic heart disease, unspecified
2537481010	Cardiac ischemia	I25.9	Chronic ischaemic heart disease, unspecified
98484016	Pulmonary embolism	I26.9	Pulmonary embolism without mention of acute cor pulmonale
1231937012	PE - Pulmonary embolism	I26.9	Pulmonary embolism without mention of acute cor pulmonale
43850011	Primary pulmonary hypertension	I27.0	Primary pulmonary hypertension
117919017	Pulmonary hypertension	I27.2	Other secondary pulmonary hypertension
146259010	Secondary pulmonary hypertension	I27.2	Other secondary pulmonary hypertension
138131012	Cor pulmonale	I27.9	Pulmonary heart disease, unspecified
81186016	Mitral valve regurgitation	I34.0	Mitral (valve) insufficiency
81192010	Mitral valve insufficiency	I34.0	Mitral (valve) insufficiency
81193017	Mitral regurgitation	I34.0	Mitral (valve) insufficiency
1230639015	MI - Mitral incompetence	I34.0	Mitral (valve) insufficiency
1230640018	MR - Mitral regurgitation	I34.0	Mitral (valve) insufficiency
1230641019	Mitral insufficiency	I34.0	Mitral (valve) insufficiency
413082017	Mitral valve anterior leaflet prolapse	I34.1	Mitral (valve) prolapse
504503012	Mitral valve posterior leaflet prolapse	I34.1	Mitral (valve) prolapse
2471474013	Mitral valve prolapse	I34.1	Mitral (valve) prolapse
2477508016	MVP - Mitral valve prolapse	I34.1	Mitral (valve) prolapse
100633013	Aortic valve stenosis	I35.0	Aortic (valve) stenosis
1232103019	Aortic stenosis	I35.0	Aortic (valve) stenosis
1232104013	AS - Aortic stenosis	I35.0	Aortic (valve) stenosis
100055018	Aortic valve regurgitation	I35.1	Aortic (valve) insufficiency
1232058018	Aortic incompetence	I35.1	Aortic (valve) insufficiency
1232060016	AR - Aortic regurgitation	I35.1	Aortic (valve) insufficiency
15387019	Aortic valve disorder	I35.8	Other aortic valve disorders
374104011	Aortic valve calcification	I35.8	Other aortic valve disorders
452008012	Aortic murmur	I35.8	Other aortic valve disorders
1235209017	Aortic valve disease	I35.9	Aortic valve disorder, unspecified
1705016	Valvular heart disease	I38	Endocarditis, valve unspecified

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
1706015	Heart valve disease	I38	Endocarditis, valve unspecified
52780013	Systolic murmur	I38	Endocarditis, valve unspecified
68333014	Chronic valvulitis	I38	Endocarditis, valve unspecified
118236017	Pansystolic murmur	I38	Endocarditis, valve unspecified
377401016	Regurgitation of common atrioventricular valve	I38	Endocarditis, valve unspecified
486555018	Disorder of heart valve	I38	Endocarditis, valve unspecified
1227366018	DM - Diastolic murmur	I38	Endocarditis, valve unspecified
1786621010	DCM - Dilated cardiomyopathy	I42.0	Dilated cardiomyopathy
494130019	HOCM - Hypertrophic obstructive cardiomyopathy	I42.1	Obstructive hypertrophic cardiomyopathy
350416016	HCM - Hypertrophic cardiomyopathy	I42.2	Other hypertrophic cardiomyopathy
93566018	Cardiopathy	I42.9	Cardiomyopathy, unspecified
142397010	Cardiomyopathy	I42.9	Cardiomyopathy, unspecified
142400018	Myocardiopathy	I42.9	Cardiomyopathy, unspecified
405112015	First degree heart block	I44.0	Atrioventricular block, first degree
1225815019	Mobitz type 2 second degree atrioventricular block	I44.1	Atrioventricular block, second degree
62986012	Left anterior fascicular block	I44.4	Left anterior fascicular block
103118017	Left posterior fascicular block	I44.5	Left posterior fascicular block
1232499017	Fascicular block	I44.6	Other and unspecified fascicular block
105498014	Left bundle branch block	I44.7	Left bundle-branch block, unspecified
1232465015	LBBB - Left bundle branch block	I44.7	Left bundle-branch block, unspecified
2646374012	ECG: LBBB - left bundle branch block	I44.7	Left bundle-branch block, unspecified
374267011	Incomplete right bundle branch block	I45.1	Other and unspecified right bundle-branch block
1231922013	RBBB - Right bundle branch block	I45.1	Other and unspecified right bundle-branch block
1232498013	BBB - Bundle branch block	I45.4	Nonspecific intraventricular block
502687018	WPW - Wolff-Parkinson-White syndrome	I45.6	Pre-excitation syndrome
350471015	Heart block	I45.9	Conduction disorder, unspecified
350487017	Cardiac arrest with successful resuscitation	I46.0	Cardiac arrest with successful resuscitation
11705016	Supraventricular tachycardia	I47.1	Supraventricular tachycardia
300104014	Atrial paroxysmal tachycardia	I47.1	Supraventricular tachycardia
413083010	Atrial tachycardia	I47.1	Supraventricular tachycardia
1232575015	SVT - Supraventricular tachycardia	I47.1	Supraventricular tachycardia
2676305017	ECG: supraventricular tachycardia	I47.1	Supraventricular tachycardia
42864016	Ventricular tachycardia	I47.2	Ventricular tachycardia
20726010	Paroxysmal tachycardia	I47.9	Paroxysmal tachycardia, unspecified
111643014	Paroxysmal supraventricular tachycardia	I47.9	Paroxysmal tachycardia, unspecified
9988012	Atrial flutter	I48	Atrial fibrillation and flutter
82343012	Atrial fibrillation	I48	Atrial fibrillation and flutter
256478018	ECG: atrial fibrillation	I48	Atrial fibrillation and flutter

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
256479014	ECG: atrial flutter	I48	Atrial fibrillation and flutter
300130013	Atrial fibrillation and flutter	I48	Atrial fibrillation and flutter
421232012	AF - Paroxysmal atrial fibrillation	I48	Atrial fibrillation and flutter
421233019	PAF - Paroxysmal atrial fibrillation	I48	Atrial fibrillation and flutter
421235014	Paroxysmal atrial fibrillation	I48	Atrial fibrillation and flutter
458527016	Rapid atrial fibrillation	I48	Atrial fibrillation and flutter
1230726010	AF - Atrial fibrillation	I48	Atrial fibrillation and flutter
2675253013	Chronic atrial fibrillation	I48	Atrial fibrillation and flutter
29302015	Ventricular premature beats	I49.3	Ventricular premature depolarisation
29303013	Ventricular premature contractions	I49.3	Ventricular premature depolarisation
45705018	Unifocal PVCs	I49.3	Ventricular premature depolarisation
374328019	Ventricular premature complex	I49.3	Ventricular premature depolarisation
1224598017	Premature ventricular complex	I49.3	Ventricular premature depolarisation
374341015	Escape beat	I49.4	Other and unspecified premature depolarisation
2164619018	Ectopic beats	I49.4	Other and unspecified premature depolarisation
60214017	Sick sinus syndrome	I49.5	Sick sinus syndrome
119267012	Sinus arrhythmia	I49.8	Other specified cardiac arrhythmias
371151012	Heart beats irregular	I49.9	Cardiac arrhythmia, unspecified
477420018	Irregular heart beat	I49.9	Cardiac arrhythmia, unspecified
1230143017	Cardiac arrhythmia	I49.9	Cardiac arrhythmia, unspecified
1230144011	Cardiac dysrhythmia	I49.9	Cardiac arrhythmia, unspecified
1230145012	Arrhythmia	I49.9	Cardiac arrhythmia, unspecified
18472010	Acute congestive heart failure	I50.0	Congestive heart failure
70653017	Congestive heart failure	I50.0	Congestive heart failure
70654011	Congestive heart disease	I50.0	Congestive heart failure
493287011	Congestive cardiac failure	I50.0	Congestive heart failure
493288018	CCF - Congestive cardiac failure	I50.0	Congestive heart failure
493289014	CHF - Congestive heart failure	I50.0	Congestive heart failure
1235017018	LVF - Left ventricular failure	I50.1	Left ventricular failure
80720010	Chronic heart failure	I50.9	Heart failure, unspecified
139475013	Heart failure	I50.9	Heart failure, unspecified
139481017	Weak heart	I50.9	Heart failure, unspecified
1234906013	HF - Heart failure	I50.9	Heart failure, unspecified
1484917012	Heart failure follow-up	I50.9	Heart failure, unspecified
2577902015	Diastolic heart failure	I50.9	Heart failure, unspecified
2645367010	Decompensated chronic heart failure	I50.9	Heart failure, unspecified
84844011	Myocarditis	I51.4	Myocarditis, unspecified
625016	Acute heart disease	I51.6	Cardiovascular disease, unspecified
37443015	Heart attack	I51.6	Cardiovascular disease, unspecified
82618012	Cardiovascular disease	I51.6	Cardiovascular disease, unspecified
206496017	Chronic disease of heart	I51.6	Cardiovascular disease, unspecified
206566012	Chronic disease of cardiovascular system	I51.6	Cardiovascular disease, unspecified
206832010	Acute cardiovascular disorder	I51.6	Cardiovascular disease, unspecified
206833017	Acute cardiovascular disease	I51.6	Cardiovascular disease, unspecified

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
497557019	Cardiac disorder	I51.6	Cardiovascular disease, unspecified
14506018	Cardiomegaly	I51.7	Cardiomegaly
92841017	Left ventricular hypertrophy	I51.7	Cardiomegaly
1231533019	LV+ - Left ventricular hypertrophy	I51.7	Cardiomegaly
1231534013	LVH - Left ventricular hypertrophy	I51.7	Cardiomegaly
93561011	Heart disease	I51.9	Heart disease, unspecified
206497014	Chronic heart disease	I51.9	Heart disease, unspecified
2764341017	Fetal heart disorder	I51.9	Heart disease, unspecified
135728018	Atherosclerosis of aorta	I70.0	Atherosclerosis of aorta
87658016	Ischemia	I70.20	Atherosclerosis of arteries of extremities, unspecified
350543011	Lower limb ischemia	I70.20	Atherosclerosis of arteries of extremities, unspecified
1787052019	PVD - Peripheral vascular disease	I70.20	Atherosclerosis of arteries of extremities, unspecified
2162392019	PVD-peripheral vascular disease	I70.20	Atherosclerosis of arteries of extremities, unspecified
48485016	Arteriosclerosis	I70.9	Generalised and unspecified atherosclerosis
64424015	Atherosclerosis	I70.9	Generalised and unspecified atherosclerosis
2816823016	Atherosclerosis of artery	I70.9	Generalised and unspecified atherosclerosis
350580017	Abdominal aortic aneurysm	I71.4	Abdominal aortic aneurysm, without mention of rupture
350581018	AAA - Abdominal aortic aneurysm	I71.4	Abdominal aortic aneurysm, without mention of rupture
111949011	Aortic aneurysm	I71.9	Aortic aneurysm of unspecified site, without mention of rupture
111952015	Aneurysm of aorta	I71.9	Aortic aneurysm of unspecified site, without mention of rupture
300496013	Raynaud's disease	I73.0	Raynaud's syndrome
395792010	Raynaud's phenomenon	I73.0	Raynaud's syndrome
477393010	Idiopathic Raynaud's phenomenon	I73.0	Raynaud's syndrome
87210015	Buerger's disease	I73.1	Thromboangiitis obliterans [Buerger]
61977017	Erythromelalgia	I73.8	Other specified peripheral vascular diseases
350534019	Peripheral ischemic vascular disease	I73.8	Other specified peripheral vascular diseases
105536013	Intermittent claudication	I73.9	Peripheral vascular disease, unspecified
350651018	Vasomotor arterial disorder	I73.9	Peripheral vascular disease, unspecified
411512011	Claudication	I73.9	Peripheral vascular disease, unspecified
1232467011	IC - Intermittent claudication	I73.9	Peripheral vascular disease, unspecified

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
1779317016	Peripheral vascular disease	I73.9	Peripheral vascular disease, unspecified
23399012	Thromboembolism	I74.9	Embolism and thrombosis of unspecified artery
63239013	Embolic infarction	I74.9	Embolism and thrombosis of unspecified artery
2695294011	Venous thromboembolic disease	I74.9	Embolism and thrombosis of unspecified artery
53457013	Vasculitis	I77.6	Arteritis, unspecified
56432011	Endarteritis	I77.6	Arteritis, unspecified
86704014	Arteritis	I77.6	Arteritis, unspecified
492264012	Arteriopath	I77.9	Disorder of arteries and arterioles, unspecified
1787050010	Peripheral arterial disease	I77.9	Disorder of arteries and arterioles, unspecified
300616016	Non-neoplastic nevus	I78.1	Naevus, non-neoplastic
300632018	Spider telangiectasis of skin	I78.1	Naevus, non-neoplastic
300634017	Spider angioma	I78.1	Naevus, non-neoplastic
412415012	Telangiectasia	I78.1	Naevus, non-neoplastic
1779210017	Rheumatoid arteritis	I79.8	Other disorders of arteries, arterioles and capillaries in diseases classified elsewhere
395800019	Superficial thrombophlebitis of leg	I80.0	Phlebitis and thrombophlebitis of superficial vessels of lower extremities
194647015	Deep venous thrombosis	I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
206384013	DVT	I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
2162148012	DVT - Deep vein thrombosis	I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
2162149016	Deep vein thrombosis	I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
2162420015	Deep venous thrombosis of leg	I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
2695919012	Wells deep vein thrombosis (DVT) clinical probability score	I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
453209018	Thrombosis of vein of lower limb	I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
158103013	Thrombophlebitis of upper extremities	I80.8	Phlebitis and thrombophlebitis of other sites
5234016	Superficial thrombophlebitis	I80.9	Phlebitis and thrombophlebitis of unspecified site
102352016	Phlebitis	I80.9	Phlebitis and thrombophlebitis of unspecified site
106650018	Thrombophlebitis	I80.9	Phlebitis and thrombophlebitis of unspecified site
300649013	Phlebitis and thrombophlebitis	I80.9	Phlebitis and thrombophlebitis of unspecified site

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
30273012	Portal vein thrombosis	I81	Portal vein thrombosis
501619010	Sagittal sinus thrombosis	I82.8	Embolism and thrombosis of other specified veins
178522012	Venous thrombosis	I82.9	Embolism and thrombosis of unspecified vein
350676017	Venous embolism	I82.9	Embolism and thrombosis of unspecified vein
2794470015	Thrombosis	I82.9	Embolism and thrombosis of unspecified vein
69942015	Varicose ulcer	I83.0	Varicose veins of lower extremities with ulcer
446271018	Varicose ulcer of lower extremity	I83.0	Varicose veins of lower extremities with ulcer
1781953019	Venous ulcer of leg	I83.0	Varicose veins of lower extremities with ulcer
2476696011	Venous ulcer	I83.0	Varicose veins of lower extremities with ulcer
59231017	Stasis dermatitis	I83.1	Varicose veins of lower extremities with inflammation
59234013	Varicose eczema	I83.1	Varicose veins of lower extremities with inflammation
157923012	Localized lipodermatosclerosis	I83.1	Varicose veins of lower extremities with inflammation
411636017	Varicose eczema leg	I83.1	Varicose veins of lower extremities with inflammation
457115011	Varicose vein of leg with phlebitis	I83.1	Varicose veins of lower extremities with inflammation
486190016	Venous eczema	I83.1	Varicose veins of lower extremities with inflammation
2471746019	Lipodermatosclerosis	I83.1	Varicose veins of lower extremities with inflammation
22052017	Varicose vein	I83.9	Varicose veins of lower extremities without ulcer or inflammation
121026013	Varicose veins of lower extremity	I83.9	Varicose veins of lower extremities without ulcer or inflammation
251690014	H/O: varicose veins	I83.9	Varicose veins of lower extremities without ulcer or inflammation
254104013	O/E - varicose veins	I83.9	Varicose veins of lower extremities without ulcer or inflammation
300726015	Bleeding varicose vein of leg	I83.9	Varicose veins of lower extremities without ulcer or inflammation
396064016	Simple varicose veins	I83.9	Varicose veins of lower extremities without ulcer or inflammation
412657010	Varices	I83.9	Varicose veins of lower extremities without ulcer or inflammation
412658017	VVs - Varicose veins	I83.9	Varicose veins of lower extremities without ulcer or inflammation

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
412659013	Varicosities	I83.9	Varicose veins of lower extremities without ulcer or inflammation
412660015	VV - Varicose veins	I83.9	Varicose veins of lower extremities without ulcer or inflammation
438270010	Varicose veins of lower extremity without ulcer AND without inflammation	I83.9	Varicose veins of lower extremities without ulcer or inflammation
459725015	Recurrent varicose veins of leg	I83.9	Varicose veins of lower extremities without ulcer or inflammation
474288018	Varicose veins	I83.9	Varicose veins of lower extremities without ulcer or inflammation
1225214014	Varicose vein observation	I83.9	Varicose veins of lower extremities without ulcer or inflammation
1788137014	VV - Varicose veins of leg	I83.9	Varicose veins of lower extremities without ulcer or inflammation

Hypertension

SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
3135013	Benign essential hypertension	I10	Essential (primary) hypertension
18632012	Benign hypertension	I10	Essential (primary) hypertension
64176011	Hypertension	I10	Essential (primary) hypertension
84112010	Hypertensive crisis	I10	Essential (primary) hypertension
87694017	Transient hypertension	I10	Essential (primary) hypertension
93494011	Systolic hypertension	I10	Essential (primary) hypertension
99042012	Essential hypertension	I10	Essential (primary) hypertension
99044013	Idiopathic hypertension	I10	Essential (primary) hypertension
99046010	Systemic primary arterial hypertension	I10	Essential (primary) hypertension
99047018	Primary hypertension	I10	Essential (primary) hypertension
103500013	Hypertensive episode	I10	Essential (primary) hypertension
116721012	Malignant hypertension	I10	Essential (primary) hypertension
251674014	H/O: hypertension	I10	Essential (primary) hypertension
405053013	Hypertension monitored	I10	Essential (primary) hypertension
413075016	Labile hypertension	I10	Essential (primary) hypertension
413076015	White coat hypertension	I10	Essential (primary) hypertension
490278018	Systemic arterial hypertension	I10	Essential (primary) hypertension
490281011	HT - Hypertension	I10	Essential (primary) hypertension
490283014	BP+ - Hypertension	I10	Essential (primary) hypertension
503982017	Accelerated essential hypertension	I10	Essential (primary) hypertension
1209829017	Labile essential hypertension	I10	Essential (primary) hypertension
1780319017	Hypertension annual review	I10	Essential (primary) hypertension
2164904016	HTN - Hypertension	I10	Essential (primary) hypertension
2694336018	Exertional hypertension	I10	Essential (primary) hypertension
2695883018	Systolic essential hypertension	I10	Essential (primary) hypertension

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
60444016	Benign hypertensive heart disease	I11.9	Hypertensive heart disease without (congestive) heart failure
107545013	Hypertensive heart disease	I11.9	Hypertensive heart disease without (congestive) heart failure
499930018	HHD - Hypertensive heart disease	I11.9	Hypertensive heart disease without (congestive) heart failure
482432016	Renal failure associated with renal vascular disease	I12.9	Hypertensive kidney disease without kidney failure
28193019	Cardiovasorenal syndrome	I13.9	Hypertensive heart and kidney disease, unspecified
178680012	Hypertension secondary to renal disease in obstetric context	I15.1	Hypertension secondary to other kidney disorders
53452019	Secondary hypertension	I15.9	Secondary hypertension, unspecified
508416019	Accelerated secondary hypertension	I15.9	Secondary hypertension, unspecified
2470031013	Benign secondary hypertension	I15.9	Secondary hypertension, unspecified

Diabetes Mellitus

SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
459172013	Type 2 diabetes mellitus with hypoglycemic coma	E11.0	Type 2 diabetes mellitus with hyperosmolarity
1488898011	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	E11.01	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycaemic-hyperosmolar coma [NKHHC]
2693962011	Hyperosmolality due to uncontrolled type 1 diabetes mellitus	E11.01	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycaemic-hyperosmolar coma [NKHHC]
2618209016	Persistent microalbuminuria associated with type II diabetes mellitus	E11.21	Type 2 diabetes mellitus with incipient diabetic nephropathy
2618210014	Persistent proteinuria associated with type II diabetes mellitus	E11.22	Type 2 diabetes mellitus with established diabetic nephropathy
2623051017	Kidney disorder associated with type 2 diabetes mellitus	E11.29	Type 2 diabetes mellitus with other specified kidney complication
9093013	Diabetic retinopathy	E11.31	Type 2 diabetes mellitus with background retinopathy
1484867016	Non proliferative diabetic retinopathy	E11.31	Type 2 diabetes mellitus with background retinopathy
1785158019	Early proliferative diabetic retinopathy	E11.33	Type 2 diabetes mellitus with proliferative retinopathy
2618240011	Diabetic cataract associated with type II diabetes mellitus	E11.36	Type 2 diabetes mellitus with diabetic cataract

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
2623027010	Neurologic disorder associated with type 2 diabetes mellitus	E11.40	Type 2 diabetes mellitus with unspecified neuropathy
2618202013	Polyneuropathy associated with type II diabetes mellitus	E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
2623035013	Polyneuropathy associated with type 2 diabetes mellitus	E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
2645899013	Diabetic autonomic neuropathy associated with type 2 diabetes mellitus	E11.43	Type 2 diabetes mellitus with diabetic autonomic neuropathy
2645962014	Diabetic gastroparesis associated with type 2 diabetes mellitus	E11.43	Type 2 diabetes mellitus with diabetic autonomic neuropathy
2694743010	Erectile dysfunction associated with type 2 diabetes mellitus	E11.43	Type 2 diabetes mellitus with diabetic autonomic neuropathy
2623025019	Neurologic complication of diabetes mellitus	E11.49	Type 2 diabetes mellitus with other specified neurological complication
292579018	Type 2 diabetes mellitus with ulcer	E11.5	Type 2 diabetes mellitus with circulatory complciation
459310018	Type 2 diabetes mellitus with arthropathy	E11.61	Type 2 diabetes mellitus with specified diabetic musculoskeletal and connective tissue complication
459313016	Type 2 diabetes mellitus with neuropathic arthropathy	E11.61	Type 2 diabetes mellitus with specified diabetic musculoskeletal and connective tissue complication
292589019	Type II diabetes mellitus - poor control	E11.65	Type 2 diabetes mellitus with poor control
292590011	Type 2 diabetes mellitus - poor control	E11.65	Type 2 diabetes mellitus with poor control
292583018	Type 2 diabetes mellitus with gangrene	E11.69	Type 2 diabetes mellitus with other specified complication
200951011	Diabetes mellitus type 2 in obese	E11.72	Type 2 diabetes mellitus with features of insulin resistance
73465010	Diabetes mellitus type II	E11.9	Type 2 diabetes mellitus without complication
73466011	Non-insulin dependent diabetes mellitus	E11.9	Type 2 diabetes mellitus without complication
80997013	Insulin resistance	E11.9	Type 2 diabetes mellitus without complication
197761014	Type 2 diabetes mellitus	E11.9	Type 2 diabetes mellitus without complication
197762019	NIDDM	E11.9	Type 2 diabetes mellitus without complication
197763012	Diabetes mellitus type 2	E11.9	Type 2 diabetes mellitus without complication
292576013	Type II diabetes mellitus with multiple complications	E11.9	Type 2 diabetes mellitus without complication
356076010	NIDDM - Insulin-treated non-insulin-dependent diabetes mellitus	E11.9	Type 2 diabetes mellitus without complication

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
356082013	Diabetes mellitus autosomal dominant type II	E11.9	Type 2 diabetes mellitus without complication
457329019	Type 2 diabetes mellitus without complication	E11.9	Type 2 diabetes mellitus without complication
457330012	Type II diabetes mellitus without complication	E11.9	Type 2 diabetes mellitus without complication
474213016	Diabetes mellitus type 2 in nonobese	E11.9	Type 2 diabetes mellitus without complication
483882011	Diabetes mellitus autosomal dominant	E11.9	Type 2 diabetes mellitus without complication
493771012	Non-insulin-dependent diabetes mellitus	E11.9	Type 2 diabetes mellitus without complication
493773010	NIDDM - Non-insulin dependent diabetes mellitus	E11.9	Type 2 diabetes mellitus without complication
493774016	Type II diabetes mellitus	E11.9	Type 2 diabetes mellitus without complication
493775015	Diabetes mellitus - adult onset	E11.9	Type 2 diabetes mellitus without complication
1223147012	Insulin treated Type II diabetes mellitus	E11.9	Type 2 diabetes mellitus without complication
1776156019	dm2	E11.9	Type 2 diabetes mellitus without complication
2620672016	Non-insulin dependent diabetes mellitus (NIDDM) in nonobese	E11.9	Type 2 diabetes mellitus without complication
15518018	Secondary diabetes mellitus	E13.9	Other specified diabetes mellitus without complication
47629018	MODY	E13.9	Other specified diabetes mellitus without complication
483885013	Mason-type diabetes	E13.9	Other specified diabetes mellitus without complication
292480018	Diabetes mellitus with hyperosmolar coma	E14.02	Unspecified diabetes mellitus with hyperosmolarity, with coma
178798017	Diabetic ketoacidosis without coma	E14.11	Unspecified diabetes mellitus with ketoacidosis, without coma
2616611010	Diabetic ketoacidosis	E14.11	Unspecified diabetes mellitus with ketoacidosis, without coma
2622192019	Ketoacidosis in diabetes mellitus	E14.11	Unspecified diabetes mellitus with ketoacidosis, without coma
354506019	Microalbuminuric diabetic nephropathy	E14.21	Unspecified diabetes mellitus with incipient diabetic nephropathy
354507011	Incipient diabetic nephropathy	E14.21	Unspecified diabetes mellitus with incipient diabetic nephropathy
456794012	Microalbuminuria	E14.21	Unspecified diabetes mellitus with incipient diabetic nephropathy
205225016	Diabetic nephropathy	E14.22	Unspecified diabetes mellitus with established diabetic nephropathy
2674163019	Diabetic glomerulonephritis	E14.22	Unspecified diabetes mellitus with established diabetic nephropathy

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
42612012	Diabetic retinal microaneurysm	E14.31	Unspecified diabetes mellitus with background retinopathy
1230610015	DR - Diabetic retinopathy	E14.31	Unspecified diabetes mellitus with background retinopathy
1785332013	Background diabetic retinopathy	E14.31	Unspecified diabetes mellitus with background retinopathy
2621399015	BDR - Background diabetic retinopathy	E14.31	Unspecified diabetes mellitus with background retinopathy
2642672017	Mild non-proliferative diabetic retinopathy	E14.31	Unspecified diabetes mellitus with background retinopathy
98476015	Proliferative diabetic retinopathy	E14.33	Unspecified diabetes mellitus with proliferative retinopathy
456706019	Proliferative diabetic retinopathy - non high risk	E14.33	Unspecified diabetes mellitus with proliferative retinopathy
456708018	Proliferative diabetic retinopathy - quiescent	E14.33	Unspecified diabetes mellitus with proliferative retinopathy
456712012	Diabetic vitreous hemorrhage	E14.33	Unspecified diabetes mellitus with proliferative retinopathy
1785154017	Preproliferative diabetic retinopathy	E14.33	Unspecified diabetes mellitus with proliferative retinopathy
2579151010	PPDR - Preproliferative diabetic retinopathy	E14.33	Unspecified diabetes mellitus with proliferative retinopathy
347657010	Diabetic maculopathy	E14.34	Unspecified diabetes mellitus with other retinopathy
456716010	Diabetic macular edema	E14.34	Unspecified diabetes mellitus with other retinopathy
458280018	Diffuse diabetic maculopathy	E14.34	Unspecified diabetes mellitus with other retinopathy
458281019	Focal diabetic maculopathy	E14.34	Unspecified diabetes mellitus with other retinopathy
1775724010	Moderate nonproliferative diabetic retinopathy	E14.34	Unspecified diabetes mellitus with other retinopathy
2579521014	NPDR - Non proliferative diabetic retinopathy	E14.34	Unspecified diabetes mellitus with other retinopathy
297550019	Acute painful diabetic neuropathy	E14.40	Unspecified diabetes mellitus with unspecified neuropathy
345486016	Diabetic neuropathy	E14.40	Unspecified diabetes mellitus with unspecified neuropathy
345487013	Diabetes mellitus with neuropathy	E14.40	Unspecified diabetes mellitus with unspecified neuropathy
473862018	Diabetic neuropathy with neurologic complication	E14.40	Unspecified diabetes mellitus with unspecified neuropathy
299011	Diabetic sensory polyneuropathy	E14.42	Unspecified diabetes mellitus with diabetic polyneuropathy
82373015	Diabetic polyneuropathy	E14.42	Unspecified diabetes mellitus with diabetic polyneuropathy
345490019	Diabetic chronic painful polyneuropathy	E14.42	Unspecified diabetes mellitus with diabetic polyneuropathy

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
57012011	Diabetic gastroparesis	E14.43	Unspecified diabetes mellitus with diabetic autonomic neuropathy
63934010	Diarrhea in diabetes	E14.43	Unspecified diabetes mellitus with diabetic autonomic neuropathy
84344019	Diabetic autonomic neuropathy	E14.43	Unspecified diabetes mellitus with diabetic autonomic neuropathy
353519012	Diabetic diarrhea	E14.43	Unspecified diabetes mellitus with diabetic autonomic neuropathy
2645902011	Diabetic peripheral neuropathy	E14.49	Unspecified diabetes mellitus with other specified neurological complication
205224017	Diabetic peripheral vascular disease	E14.51	Unspecified diabetes mellitus with peripheral angiopathy, without gangrene
473994010	Diabetes with peripheral circulatory disorders	E14.51	Unspecified diabetes mellitus with peripheral angiopathy, without gangrene
309740011	Diabetic neuropathic arthropathy	E14.61	Unspecified diabetes mellitus with specified diabetic musculoskeletal and connective tissue complication
93774015	Necrobiosis lipoidica diabeticorum	E14.62	Unspecified diabetes mellitus with specified skin and subcutaneous tissue complication
358149019	Diabetic dermopathy	E14.62	Unspecified diabetes mellitus with specified skin and subcutaneous tissue complication
401531012	Diabetic - poor control	E14.65	Unspecified diabetes mellitus with poor control
2164250010	Unstable diabetes mellitus	E14.65	Unspecified diabetes mellitus with poor control
2618214017	Diabetic skin ulcer	E14.69	Unspecified diabetes mellitus with other specified complication
2623058011	Skin ulcer associated with diabetes mellitus	E14.69	Unspecified diabetes mellitus with other specified complication
309179013	Neuropathic diabetic ulcer - foot	E14.73	Unspecified diabetes mellitus with foot ulcer due to multiple causes
417658010	Diabetic foot	E14.73	Unspecified diabetes mellitus with foot ulcer due to multiple causes
1209795012	Diabetic foot ulcer	E14.73	Unspecified diabetes mellitus with foot ulcer due to multiple causes
2532976019	O/E - left chronic diabetic foot ulcer	E14.73	Unspecified diabetes mellitus with foot ulcer due to multiple causes
2576753016	Infection of foot associated with diabetes	E14.73	Unspecified diabetes mellitus with foot ulcer due to multiple causes
121589010	Diabetes mellitus	E14.9	Unspecified diabetes mellitus without complication
178796018	Diabetes mellitus without complication	E14.9	Unspecified diabetes mellitus without complication

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
251591016	H/O: diabetes mellitus	E14.9	Unspecified diabetes mellitus without complication
264682013	Diabetic on insulin	E14.9	Unspecified diabetes mellitus without complication
356120017	Diabetic severe hyperglycemia	E14.9	Unspecified diabetes mellitus without complication
384879010	dm	E14.9	Unspecified diabetes mellitus without complication
405057014	Diabetes monitored	E14.9	Unspecified diabetes mellitus without complication
502372015	DM - Diabetes mellitus	E14.9	Unspecified diabetes mellitus without complication
2157525015	Newly diagnosed diabetes	E14.9	Unspecified diabetes mellitus without complication

Asthma

SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
1483199016	Allergic asthma	J45.0	Predominantly allergic asthma
1493644014	Atopic asthma	J45.0	Predominantly allergic asthma
1493645010	Allergic atopic asthma	J45.0	Predominantly allergic asthma
50801012	Allergic-infective asthma	J45.9	Asthma, Unspecified
52467014	Exercise-induced asthma	J45.9	Asthma, Unspecified
56808014	Bakers' asthma	J45.9	Asthma, Unspecified
93175011	Asthmatic breathing	J45.9	Asthma, Unspecified
112042019	Hay asthma	J45.9	Asthma, Unspecified
147740015	Chronic allergic bronchitis	J45.9	Asthma, Unspecified
301479016	Asthmatic	J45.9	Asthma, Unspecified
301480018	Bronchial asthma	J45.9	Asthma, Unspecified
301485011	Asthma	J45.9	Asthma, Unspecified
301509017	Mixed asthma	J45.9	Asthma, Unspecified
338238011	Brittle asthma	J45.9	Asthma, Unspecified
350148014	Late onset asthma	J45.9	Asthma, Unspecified
396119015	Asthma attack	J45.9	Asthma, Unspecified
419210017	Exacerbation of asthma	J45.9	Asthma, Unspecified
419211018	Acute exacerbation of asthma	J45.9	Asthma, Unspecified
446841017	Acute asthma	J45.9	Asthma, Unspecified
456163018	Asthma - currently active	J45.9	Asthma, Unspecified
1208969012	Mild asthma	J45.9	Asthma, Unspecified
1208972017	Severe asthma	J45.9	Asthma, Unspecified
1227504017	EIA - Exercise-induced asthma	J45.9	Asthma, Unspecified
2157501011	Allergic bronchitis	J45.9	Asthma, Unspecified
2471432015	Cough variant asthma	J45.9	Asthma, Unspecified
2674136015	Intermittent asthma	J45.9	Asthma, Unspecified
2674137012	Mild intermittent asthma	J45.9	Asthma, Unspecified

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SNOMED CT Code	Snomed CT Description	ICD-10 AM code	ICD-10 AM Description
2674138019	Mild persistent asthma	J45.9	Asthma, Unspecified
2674139010	Moderate persistent asthma	J45.9	Asthma, Unspecified
2674141011	Exacerbation of intermittent asthma	J45.9	Asthma, Unspecified
2674142016	Exacerbation of persistent asthma	J45.9	Asthma, Unspecified
2818419010	Acute exacerbation of chronic asthmatic bronchitis	J45.9	Asthma, Unspecified
198754012	Status asthmaticus	J46	Status asthmaticus
1231735012	Acute severe asthma	J46	Status asthmaticus

The list of Vitamin D replacement medications used in PHCC

Medication
Vitamin D2 (Ergocalciferol) 50,000 units
Vitamin D2 (Ergocalciferol) 50,000 units TAB
Vitamin D2 (Ergocalciferol) 1,000 units
Vitamin D2 (Ergocalciferol) 1,000 units CAP
Vitamin D2 (Ergocalciferol) 50,000 units
Vitamin D2 (Ergocalciferol) 600,000 units /1.5 mL INJ
Vitamin D2 (Ergocalciferol) 500 units CAP
Vitamin D2 (Ergocalciferol) 500 units
Vitamin D3 (Cholecalciferol) 300,000 units/mL (1 mL) INJ
Vitamin D2 (Ergocalciferol) 300,000 units/mL (1 mL) INJ
Vitamin D3 (Cholecalciferol) 4500 units/mL (10 mL) Oral DROP
Alfacalcidol 2 mcg/mL (0.5 mL) INJ
Vitamin D2 (Ergocalciferol) 1,000 units
Vitamin D2 (Ergocalciferol) 500 units
Vitamin D3 (Cholecalciferol) 4500 units/mL (10 mL) Oral
Vitamin D3 (Cholecalciferol) 4500 units/mL (10 mL) Oral Drops

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Item	Item number	STROBE Items	RECORD Items	Showing compliance with requirements in the current study
Title and Abstract				
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	All the requirements were attended in the title and the abstract (page 1 and 2)
Introduction				
Background rationale	2	Explain the scientific background and rationale for the investigation being reported.		Verified. The last paragraph of "Introduction chapter" on page 4 highlights the rationale.
Objectives	3	State specific objectives, including any prespecified hypotheses.		Objectives are SMART and a study hypothesis was specified in the last paragraph of "Introduction chapter" on page 4
Methods				
Study Design	4	Present key elements of study design early in the paper.		Completed (Methodology on Page 4)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Completed (Methodology on Page 4)
Participants	6	(a) Cohort study: Give the eligibility criteria and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study: Give the eligibility criteria and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross-sectional study: Give the eligibility criteria and the sources and methods of selection of participants. (b) Cohort study:	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be	The data collection part of methodology defines the codes and algorithms for data extraction (page 4 and 5 and appendix A) No specific validation procedure is used apart from the continuous quality checks by the Health Information Management Department of PHCC responsible for the electronic health recording system management at the organizational level. The code translation between SNOMED and

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		For matched studies, give matching criteria and number of exposed and unexposed. Case-control study: For matched studies, give matching criteria and the number of controls per case.	provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	ICD-10 is updated on a monthly basis. No linkage is required in the current study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	The data collection part of methodology defines the codes and algorithms for data extraction (page 4 and 5 and appendix A)
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Appendix A
Bias	9	Describe any efforts to address potential sources of bias.		Study limitation on page 2, and in the end of discussion on page 14 and 15.
Study size	10	Explain how the study size was arrived at.		Already described in Methodology (Methodology-Study population – Page 4)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Data Analysis chapter on page 5 provides a description on how quantitative variables were handled.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study: If applicable, explain how loss to follow-up was addressed. Case-control study: If applicable, explain how matching of cases and controls was addressed. Cross-sectional study: If applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.		Data Analysis chapter on page 5 provides a description of statistical methods used.
Data access and cleaning methods		N/A	RECORD 12.1: Authors should describe the extent to which the investigators had access to the	The investigator was provided with the full list of variables requested for the whole study population with the filters

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			database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	specified. This was mentioned in Data Collection paragraph on page 4 and 5 of the manuscript. Data Analysis chapter on page 5 provides a description on methods for data cleaning.
Linkage		N/A	RECORD 12.3: State whether the study included person level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	No data linkage was needed.
Results				
Participants	13	(a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed). (b) Give reasons for nonparticipation at each stage. (c) Consider use of a flow diagram.	RECORD 13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	A total of 421,283 adults (in the study specified age intervals) accessed primary healthcare services in 2017. Out of those active users only 102,342 individuals had a valid serum vitamin D measurement during the one-year study period. Refer to Data Collection paragraph on page 4 and 5 of the manuscript.
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, and social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study: summarize follow-up time (e.g., average and total amount).		Table 1 in the results chapter on page 6 of the manuscript describes the study population analyzed.
Outcome data	15	Cohort study: Report numbers of outcome events or summary measures over time. Case-control study: Report numbers in each exposure category or summary measures of exposure. Cross-sectional study: Report numbers of outcome events or summary measures.		Verified in Results chapter
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries		Verified in Results chapter

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		when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions and sensitivity analyses		
Discussion				
Key results	18	Summarize key results with reference to study objectives.		Verified
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	The study limitations were written after the abstract on page 2 in line with the journal requirements. The study limitations have also been discussed at the end of discussion chapter of the manuscript on page 14 and 15.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		
Generalizability	21	Discuss the generalizability (external validity) of the study results.		This was discussed with limitations at the end of discussion chapter of the manuscript on page 14 and 15.
Other Information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		No funding was requested or received for the current study.
Accessibility of protocol, raw data, and programming code		N/A	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	The research team signed a confidentiality agreement with PHCC and therefore no access to raw data is allowed by a third party. The study protocol can be provided as a supplementary info if requested by journal. In addition, the codes and algorithms for data extraction are provided in appendix A.

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