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Vitamin D deficiency in Kazakhstan: cross-sectional study

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Vitamin D deficiency in Kazakhstan: cross-sectional study

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Abstract

Vitamin D deficiency (VDD) is one of the serious and highly debatable public health problems affecting at least one billion of world population. This study objected to evaluate Vitamin D status in adult population of both sexes residing in different geographical areas of Kazakhstan and to elucidate the possible contributing factors related to VDD.

This cross-sectional study covered 6 regions of Kazakhstan and applied the systematic random sampling to recruit 1,347 healthy adults (of whom 819 were females) with mean age 44±14 years. The concentration of 25-hydroxy vitamin D (25-OHD) was measured from May 2018 to August 2018 with Architect 25OH Vitamin D assay (Abbott Ireland Diagnostics Division Lisnamuck, Longford Co. Longford Ireland). Vitamin D deficiency was defined as 25-OHD values not exceeding 20 ng/mL as a reference threshold in healthy population.

The median serum 25(OH)D concentrations in all studied regions of Kazakhstan were below the reference threshold (20 ng/mL). The lowest range of vitamin D (<10 ng/mL) was observed more commonly in females (34.6 % – 283) as compared to males (16.7 % – 88) and was significantly higher in Asians (33.2 % – 352) in contrast with Caucasians (6.7 % – 19) ($\chi 2$=177,939; D.f.=3; p-value=<0,001). The proportion of severe VDD was higher in individuals with low body mass index (31.1 % – 188) vs. individuals with high body mass index (18.7 % – 50). In this study individuals aged 60 years and older had the most favorable situation with 25-OHD concentrations since these were normal in 14.4 % of observations ($\chi 2$=26,589; D.f.=6; p-value=<0,001).

Studying the prevalence of VDD is an important public health task. Further research is needed to understand the epidemiology of VDD in more details to tailor intervention programs.

Key words

Adults; Cross-sectional study; Vitamin D deficiency; Kazakhstan

Introduction

Globally, Vitamin D deficiency (VDD) remains one of the unresolved public health issues affecting at least one billion of world population [1]. Prevalence of vitamin D deficiency in the northern hemisphere gets even higher in winter, with decreased insolation [2] and remains unresolved even with daily intake of vitamin complexes, drinking of a glass of milk and eating salmon [3]. Although people residing near the equator and not protecting their skin from sunlight have adequate levels of Vitamin D [4], others living even in the sunniest world's countries and shielding most of their skin, are affected by VDD [5].

In fact, Vitamin D presents a family of fat-soluble vitamins, of which 25-hydroxyvitamin D_3 (cholecalciferol) and 25-hydroxyvitamin D_2 (ergocalciferol) are the most important for humans. Vitamin D is responsible for a range of physiological effects, including absorption of calcium, magnesium, and phosphorous in small intestine [6]. Vitamin D could be obtained both through a direct synthesis in human skin following exposure to a sunlight (wavelength 290 to 315 nm) or through a diet containing Vitamin D-rich products (primarily dairy products and oily fish). Vitamin D status could be evaluated by means of 25-hydroxyvitamin D (25(OH)D), which is synthetized in liver and is metabolized in kidneys to 1.25-dihydroxyvitamin D [7].

However, to judge about the prevalence of VDD properly, the issue of definition is of utmost importance. Although there is no unified classification related to Vitamin D status, the serum level of 25(OH)D below 10 ng/mL (25 nmol/L) is considered to be deficient by a number of international clinical guidelines [2, 8]. Nevertheless, the Institute of Medicine [9] states that serum levels of 25(OH)D should not drop below 20 ng/mL (50 nmol/L), while according to the Endocrine Society [2], to achieve optimal skeletal health and muscle strength, the serum levels of 25(OH)D should be at least 30 ng/mL (75 nmol/L). Still, it has to be noted that the Endocrine Society guidance relates to patient populations while for a healthy adult population the threshold of 30 ng/mL is not applicable and an individual threshold of 20 ng/mL (50 nmol/L) should be used instead. The cut-off of 30 ng/mL was selected based on the findings that serum PTH begins to plateau and maximum calcium absorption occurs when 25(OH)D reaches the level of 30–40 ng/mL [10], and that this level reduces the risk for falls [11]. In their Practice Guidelines on Vitamin D, the Endocrine Society went further and defined VDD as the serum 25(OH)D < 20 ng/mL, and insufficiency as 21–29 ng/mL [2].

Over the past decade of years numerous studies evaluating the vitamin D status in countries across the world were performed. Still, to the best of our knowledge, none of them described the situation in Kazakhstan – a Central-Asian state located at longitude from 46.490 to 87.310 E and at latitude from 40.670 to 54.905 N. The country has a markedly continental climate with approximately 200 sunny days a year for most of its territory [12]. The population of Kazakhstan is around 18.3 million people and being the ninth largest world country, Kazakhstan has one of the lowest population densities (6 people per square kilometer). The country is composed of 14 regions that could be geographically divided into eastern provinces (East Kazakhstan and Pavlodar regions), central provinces (Karaganda and Akmola regions), northern provinces (North Kazakhstan and Kostanay regions), western provinces (West Kazakhstan, Aktobe, Atyrau and Mangystau regions), and southern provinces (South Kazakhstan, Almaty, Zhambyl and Kyzylorda regions). Besides, Kazakhstan has three so-called "cities of republican significance" – Nur-Sultan, Almaty and Shymkent that administratively are considered to be equal to a region [13]. The majority of population (56 %) resides in urban areas and the proportion of women makes up 51.7 %. Kazakhstan is one of the most industrialized countries in the world possessing ample natural resources [14]. The total fertility rates vary between the country's regions being the highest (>3.2) in more religious southern provinces [15].

The aim of this study was to evaluate Vitamin D status in adult population of both sexes residing in different geographical areas of Kazakhstan and to elucidate the possible contributing factors related to VDD.

Materials and methods

This cross-sectional study enrolled 1,347 healthy adults (out of them 819 were females), residing in 6 regions of Kazakhstan with a mean age of 44±14 years, who attended a single-consultation outpatient clinic for routine check-up. The systematic random sampling was applied to select 10-15 patients per day from each region during summer months (from May 2018 to August 2018). General characteristics of the study participants are presented in Table 1.

Table 1: General characteristics of the study participants (N=1,347)

Variables		N	%
Sex	Female	819	60.8 %
	Male	528	39.2 %
Ethnicity	Caucasian (Russian)	285	21.2 %
	Asian (Kazakh)	1,061	78.8 %
*BMI	< 25.0	604	44.8 %
	25.0-29.9	476	35.3 %
	=> 30.0	267	19.8 %
Age (Median and 25^{th}; 75^{th} percentiles)		43 (33; 55)	
Age group, years	18-39	589	43.7 %
	40-59	570	42.3 %
	=> 60	188	14.0 %
Concentration of 25(OH)D (Median and 25^{th}; 75^{th} percentiles)		15,00 (10; 22,00)	
Status of serum 25(OH)D levels	< 20 ng/mL	943	70.0 %
	=> 20 ng/mL	404	30.0 %
Total amount		1,347	100.0 %
*BMI – Body Mass Index			

The exclusion criteria were: (1) presence of any acute or chronic severe somatic pathology, including hepatic or renal disease, metabolic bone disease, type 1 diabetes, malignancy, (2) history of recent immobility for a period of more than one week, (3) pregnancy and lactation, (4) current dieting or consumption of multivitamin supplements containing vitamin D or its combinations.

Selection of study regions was made to enable adequate representation of all geographical areas of Kazakhstan with the exception of northern provinces, where D(25-OHD) assay was unavailable. Figure 1 demonstrates the proportion of individuals enrolled from different country regions.

Biochemical analysis

Blood sampling was performed between 8:00 and 10:00 a.m. in a network of governmentally licensed laboratories entitled “IN VITRO”, which operate in all study regions. After disinfection of hands and venipuncture, blood was drawn into a test tube with subsequent centrifugation and storage at -20 °C.

Concentrations of serum 25-hydroxy vitamin D(25-OHD) were measured with Architect 25OH Vitamin D assay and expressed in ng/mL.

The Architect (Abbott Ireland Diagnostics Division Lisnamuck, Longford Co. Longford Ireland) 25OH Vitamin D assay (5P02 ARCHITECT 25-OH Vitamin D Reagent Kit) is a delayed 1-step chemiluminescence microparticle immunoassay (CMIA) that includes automated online pre-treatment with flexible assay protocols (Chemiflex). The test uses microparticles coated with a polyclonal sheep anti-vitamin D IgG antibody, and a biotinylated vitamin D anti-biotin IgG acridinium-labelled conjugate complex for the quantitative determination of 25(OH)D2 and D3 in human serum and plasma.

External and Internal Quality Control Procedures for analyzing 25(OH)D levels

All IN VITRO laboratories utilize the Vitamin D Standardization Program (VDSP), which is certified according to Standard Reference Material 2972 of the National Institute of Standards and Technology (SRM 2972 NIST). IN VITRO laboratories successfully passed the performance criterion of ±5 % mean bias of the Centers for Disease Control and Prevention (CDC) and University of Ghent Vitamin D2 and D3 Reference Method with an overall imprecision of <10% over the concentration from 22 to 275 nmol/L for total 25-hydroxyvitamin D [16].

All IN VITRO laboratories have standardized procedures to test for serum 25(OH)D levels, which are based on the analysis of panels obtained from representative sample of population. The target range for 25(OH)D is 30 to 40 ng/ml (75 – 100 nmol/L). The reference range varied from 30 to 100 ng/ml with respect to geographical, seasonal, populational, and nutritional characteristics as well as environmental factors. As the gold standard, all IN VITRO laboratories adopted a mean range that was analyzed with liquid chromatography-mass spectrometry (LC-MS). The vast majority (96 %) of results obtained from all IN VITRO laboratories have fallen within ± 25 % of the target values and were not significantly different from the mean values analyzed with LC-MS. The laboratories are standardized between themselves according to a strict quality control system (ISO15189:2012, ISO15189:2007) and standard operating procedures (SOP). External quality control for harmonization of 25(OH)D test results between different laboratories is provided by means of audits from the side of responsible agency – Ministry of Healthcare of the Republic of Kazakhstan – that are conducted to ensure the compliance with ICH GCP and GLP standards.

Quality control of the ARCHITECT 25-OH Vitamin D assay consisted of testing for one repetition of each control level every 24 hours of operation after performing calibration and service procedures or maintenance, which may affect the test performance. Each laboratory independently set its own control ranges to monitor the test performance. If the control value was outside the specified range, the corresponding test results were considered to be invalid. In such cases, re-testing and re-calibration were carried out. To establish control ranges, each laboratory independently set the target concentration and concentration ranges for new control series at each level of clinically significant concentration of serum 25(OH)D. The procedure included at least 20 test repetitions performed over several (3-5) days with further determination of the expected average (target) values and variability of these average values based on the results obtained.

General recommendations for quality control are implemented in accordance with the Clinical and Laboratory Standards Institute (CLSI) Document C24-AZ and other published guidelines (Clinical and Laboratory Standards Institute (CLSI). Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline–Third Edition. CLSI Document C24-A3. Wayne. PA: CLSI; 2006) [17].

Definition of vitamin D deficiency

Vitamin D deficiency was defined as 25-OHD values not exceeding 20 ng/mL as a reference threshold. It was a target, which was achieved by many in the current healthy population [18].

Statistical analysis

Statistical analyses was processed in SPSS 20.0 for Windows. Firstly, the type of data distribution was tested and descriptive statistics of numerical variables was evaluated. Because the data distribution was different from normal, descriptive statistics were generated by computing median and the respective 25 and 75 percentile boundaries. Kruskal-Wallis test (H) was applied to enable comparisons between study groups. Qualitative variables were presented in absolute numbers and their percentages. Pearson's chi-square ($\chi2$) test was used to evaluate difference of the frequencies in groups. The critical value was considered significant at $p < 0.05$.

Ethics

All the study participants signed voluntary informed consent before participation. The study was approved by the Ethics Committee of the Non-Profit Joint-Stock Company Astana Medical University (Protocol No 6, February 15th, 2018).

Results

The median serum 25(OH)D concentrations in all studied regions of Kazakhstan were below the reference threshold (20 ng/mL). In two southern provinces – Almaty and South Kazakhstan regions – the median serum 25(OH)D levels were 18.0 (12.00; 24.00) ng/mL and 16.0 (11.00; 22.00) ng/mL, respectively. Meanwhile, the central provinces of Kazakhstan had median rates of 25(OH)D equal to 18 (11.0; 26.0) ng/mL in Karaganda region and to 11 (8.00;18.00) ng/mL in Akmola region. The population of western Kazakhstan province – Aktobe region – was also characterized by the low median level of 25(OH)D, which was found to be 12.00 (9.00; 12.00) ng/mL. Eastern part of the country was represented by Pavlodar region, which had the median range of 25(OH)D equal to 14 (10.00; 19.00) ng/mL. Such, we revealed significant differences in median ranges of 25(OH)D between the study regions (H=85.162; D.f.=5; p<0.001) (Figure 2).

We found out that low vitamin D status (<20 ng/mL) was more common among females (647 – 79.0 %) as compared to males (296 –56.1 %) ($\chi2$=80.447; D.f.=1; p=<0.001). Asians, who constitute the bulk of Kazakhstani population have significantly higher rates of VDD equal to 77.9 % (827 individuals) as compared to Caucasians, who had lower rates of VDD (40.4 % – 115 individuals) ($\chi2$=151.154; D.f.=1; p=<0.001). The most affected by VDD was the group aged between 40 and 59 years, in which the proportion of individuals with normal range of serum 25(OH)D was as low as 5.6 %. The most favorable situation was observed in the age group of 60 years and over, where 25(OH)D concentrations were normal in 14.4 % of individuals ($\chi2$=26.589; D.f.=6; p=<0.001). Of interest was the fact that the proportion of individuals with VDD among those who had body mass index (BMI) < 25.0 was almost the same as among those who had BMI => 30.0 and composed 70.7 % and 70.0 %, respectively ($\chi2$=3.360; D.f.=2; p=0.186). Also, we failed to find any difference in 25(OH)D concentrations between representatives of different income groups ($\chi2$=0.130; D.f.=1; p=0.719) (Table 2).

Most people in our study (42.4 %) had vitamin D status in the range from 10 to 20 ng/mL and nearly one third (27.5 %) of them had serum 25(OH)D concentrations below 10 ng/mL. Females had deficient vitamin D status (<10 ng/mL) two times more often than males. Similarly, males had sufficient serum 25(OH)D concentrations (20-30 ng/mL) 2.5 times more frequently than females. There was no much variation in serum 25(OH)D concentrations across different age groups at the cut-offs of <10 ng/mL and of 10-20 ng/mL. Still, the proportion of individuals having 25(OH)D concentrations in the range from 20 to 30 ng/mL were almost two times smaller in the older age group (=> 60 years). Surprisingly, the same age group had 2 times more often serum 25(OH)D concentrations above 30 ng/mL (Table 3).

Table 2: Characteristics of vitamin D status in adult Kazakhstani population (n=1347)

Variables	Status of 25(OH)D in serum				Test of difference		
	=> 20 ng/mL		<20 ng/mL		$\chi 2$	D.f.	p
	N	%	N	%			
Sex							
Female	172	21.0 %	647	79.0 %	80.447	1	<0.001
Male	232	43.9 %	296	56.1 %			
Ethnicity							
Caucasian (Russian)	170	59.6 %	115	40.4 %	151.154	1	<0.001
Asian (Kazakh)	234	22.1 %	827	77.9 %			
Age group, years							
18-39	186	31.6 %	403	68.4 %	1.812	2	0.404
40-59	168	29.5 %	402	70.5 %			
=> 60	50	26.6 %	138	73.4 %			
BMI group							
< 25.0	177	29.3 %	427	70.7 %	3.360	2	0.186
25.0-29.9	156	32.8 %	320	67.2 %			
=> 30.0	404	30.0 %	943	70.0 %			
Monthly income*							
Salary above the median range	104	30.8 %	234	69.2 %	0.130	1	0.719
Salary below the median range	300	29.7 %	709	70.3 %			
*According to the 2017 report of the national Committee on Statistics, the median salary in Kazakhstan constituted 83,000 Tenge, which was equivalent to 254.6 USD [19]							

Table 3. Different status of vitamin D in adult Kazakhstani population by sex and age (n=1347)

	Status of 25(OH)D in serum							
	< 10 ng/ml		10-20 ng/ml		20-30 ng/ml		> 30 ng/ml	
	N	%	N	%	N	%	N	%
Sex								
Female	283	34.6	363	44.3	105	12.8	68	8.3
Male	88	16.7	208	39.4	184	34.8	48	9.1
Age group, years								
18-39	157	26.7	245	41.6	130	22.1	57	9.7
40-59	151	26.5	251	44.0	136	23.9	32	5.6
=> 60	63	33.5	75	39.9	23	12.2	27	14.4
Total population	371	27.5	571	42.4	289	21.5	116	8.6

Discussion

This study aimed at evaluation of VDD rates amongst adults residing in different regions of the Republic of Kazakhstan representing different geographical areas and at identification of the possible contributing factors related to VDD. The major finding of this study was a high rate of VDD as two thirds of study participants had serum 25(OH)D concentrations below 20 ng/mL, while not more than 10 % of them had optimal levels of serum 25(OH)D defined as 30 ng/mL (75 nmol/L). Female gender, younger age, high BMI and residence in provinces further north were the major contributing factors for VDD.

As various studies on VDD use various assays, a significant variation may occur and up to a quarter of the screened population may be regarded as in need of treatment [20]. Notwithstanding that immunoassays have been commonly used for testing the serum level of 25(OH)D, tandem mass spectrometry has been recently recognized as the gold standard due to its higher precision. Also, it enables separate detection of 25(OH)D_2 and 25(OH)D_3 [21]. Besides, the National Institute of Standardization Technology provides standards for the Vitamin D Standardization Program and frozen samples from the previous studies are also available for standardization of the existing serum 25(OH)D data [22]. All this helps to decrease non-objectivity of the serum 25(OH)D measurement between different studies coming from different populations.

Unfortunately, there is a lack of published evidence from Kazakhstan regarding the magnitude of VDD among adults. Nugmanova et al. investigated associations between Vitamin D status and human immunodeficiency virus (HIV) viral load. Although this study failed to confirm such relationship, the median serum level of 25(OH)D was 24.42 [23]. Algazina et al. evaluated serum levels of 25(OH)D in patients with skin disorders (acne and psoriasis) in comparison with healthy controls on a small sample consisting of 66 individuals. According to this study, the majority of healthy controls (88.5 %) had normal values of 25(OH)D (≥ 30 ng/mL), while 40 % of dermatology patients had vitamin D insufficiency and 35 % were deficient or had serum 25(OH)D below 20 ng/mL [24]. A number of studies evaluated the rate of arterial hypertension [25, 26] and depression [27, 28] in residents of central and eastern provinces located at higher latitudes as compared to Southern provinces. Although the status of Vitamin D was not assessed as a part of these surveys, one might hypothesize that increased rates of arterial hypertension and depression maybe partly attributed to low serum levels of 25(OH)D.

Low exposure to sun rays is considered to be the major cause of VDD. In Kazakhstan the sunshine duration is 2,200 to 3,000 hours per year, which is comparable with that in the USA, India, China, Mongolia, most of the territory of Australia and South Africa [29]. Southern and central provinces of Kazakhstan get 1300 – 1800 kWh per square meter of solar radiation per year, while eastern, western and northern provinces have around 1000 – 15000 kWh per square meter per year [30]. However, to interpreter these findings accurately, it is important to consider the duration of frost-free season in Kazakhstan, which lasts 140-170 days per year in southern provinces and 90-100 days per year in the rest of the country. With the average annual air temperature ranging between +2.4^0 C in northern provinces and +13.5^0 C in southern provinces, people have to cover their bodies most of the year, leaving only faces exposed to sun [31]. Because sun-avoiding behavior has become extensively popular in Kazakhstan, the obtaining of sufficient exposure to sunlight to enable adequate production of vitamin D_3 is even more problematic.

Consumption of oily fish, in particular salmon or herring and cod liver oil serve as major dietary sources of vitamin D. Still, very few traditional cuisines in the world are able to maintain the sufficient vitamin D intake [32]. In Kazakhstan the bulk of traditional diet consists of meat, flour and dairy products, with very little addition of non-oily fish. While there is a high awareness of the problems associated with VDD in young children and pediatricians commonly recommend the intake of fish oil or vitamin D supplements in children until the age of 3 years, certain categories of disadvantaged children continue to suffer from VDD [33]. Although food fortification with Vitamin D is not practiced, addition of 25(OH)D_3 into commercial bird feeds is common at the poultry farms that helps to increase the muscle content of 25(OH)D3 in chicken [6].

It might prove to be useful to compare the data of the present study with standardized surveillance data from other international locations. Such, the weighted percentage of serum 25(OH)D concentrations below 20 ng/mL in the entire USA population during the summer months was 17 %, while that during the winter months was 35 %. At the same time, the weighted percentage of serum 25(OH)D concentrations below 30 ng/mL was seen in 57 % of the USA population during the summer months as compared to 75 % during the winter months [34]. According to Canadian Health Measures survey, just one third (32 %) of Canadians had 25(OH)D concentrations below 20 ng/mL, and during adulthood this proportion was the lowest (25 %) among individuals aged 60 to 79 years, which corresponds with the findings of our study [35]. As for the European Union countries, there is a significant variation in prevalence of VDD, which appeared to be dependent on the country latitude. Thus, 25(OH)D concentrations below 10 ng/mL were less prevalent in the more northerly latitude countries such as Iceland (7.0 % of adult population) as compared with the more mid-latitude countries such as the United Kingdom (21.8 % of adult population) [36]. The most likely explanation to this phenomenon is that more northerly latitude countries use Vitamin D supplementation and/or fortification more commonly. In central and eastern European countries such as Poland, 65.8 % of adults have 25(OH)D levels of less than 20 ng/ml, while 89.9 % of the country population have 25(OH)D levels of less than 30 ng/ml. Similar to our findings, obesity and younger age were associated with lower 25(OH)D concentrations [37].

Certainly, our study is not fully representative of the whole republic, due to the limited data collection in rural regions. In fact, our study can be declared as a pilot. The foundation of this work may be the first step for implementation of the large-scale epidemiological studies targeted on assessment of nutrient status in Kazakhstani population and on prevalence evaluation of such important health problems as vitamin D deficiency and iron-deficiency anemia [38]. However, a major drawback of this study is that sample collection proceeded during the summer months only and that this potentially presents an overly positive slant on the status values shown.

Conclusion

High prevalence of VDD remains an important problem in countries of northern hemisphere especially in winter months. The most predisposed population groups are elderlies, pregnant and postmenopausal women, obese children, people with increased skin pigmentation, and individuals avoiding direct exposure to sunlight. According to the study findings, there was a remarkably high rate of VDD as two thirds of study participants had serum 25(OH)D concentrations below 20 ng/mL, which is internationally recognized as an optimal level for healthy population. Based on the fact that blood samples were collected exclusively during the summer months, the magnitude of this problem is likely to be even greater. Females, individuals of younger age or those having high BMI were found to have higher rates of VDD. Thus, the studies on prevalence of VDD present an important public health task for medical professionals of the Kazakhstan Republic. Further research is needed to understand the epidemiology of VDD in more details in order to tailor intervention programs successfully.

Contributors

All authors have contributed to manuscript writing and review, and have approved the final version.

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Conflict of interest statement

No conflict of interest for any of the authors.

Author statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication

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References

1. Holick MF: High prevalence of vitamin D inadequacy and implications for health. In: *Mayo Clinic Proceedings: 2006*: Elsevier; 2006: 353-373.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM: Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism* 2011, 96(7):1911-1930.
3. Tangpricha V, Pearce EN, Chen TC, Holick MF: Vitamin D insufficiency among free-living healthy young adults. *The American journal of medicine* 2002, 112(8):659-662.
4. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Doughertly C, Gunter EW, Bowman BA: Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. *The American journal of clinical nutrition* 2002, 76(1):187-192.
5. Van Schoor N, Lips P: Global overview of vitamin D status. *Endocrinology and Metabolism Clinics* 2017, 46(4):845-870.
6. Holick MF: The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. *Reviews in Endocrine and Metabolic Disorders* 2017, 18(2):153-165.
7. Holick MF: Resurrection of vitamin D deficiency and rickets. *The Journal of clinical investigation* 2006, 116(8):2062-2072.
8. Outcome of a public consultation on the Draft Scientific Opinion of the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) on Dietary Reference Values for vitamin D. EFSA supporting publication. In., vol. EN-1078: EFSA (European Food Safety Authority); 2016: 100.
9. Ross AC: The 2011 report on dietary reference intakes for calcium and vitamin D. *Public health nutrition* 2011, 14(5):938-939.
10. Valcour A, Blocki F, Hawkins DM, Rao SD: Effects of age and serum 25-OH-vitamin D on serum parathyroid hormone levels. *The Journal of Clinical Endocrinology & Metabolism* 2012, 97(11):3989-3995.
11. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM: Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. *The Journal of Clinical Endocrinology & Metabolism* 2012, 97(4):1153-1158.
12. Pavlovic Z, Gritzner CF: Kazakhstan: Infobase Publishing; 2009.
13. Kazakhstan, Unitary County, available at: https://www.oecd.org/regional/regional-policy/profile-Kazakhzstan.pdf (accessed 1 August 2019).
14. Semenova Y, Zhunussov Y, Pivina L, Abisheva A, Tinkov A, Belikhina T, Skalny A, Zhanaspayev M, Bulegenov T, Glushkova N: Trace element biomonitoring in hair and blood of occupationally unexposed population residing in polluted areas of East Kazakhstan and Pavlodar regions. *Journal of Trace Elements in Medicine and Biology* 2019, 56:31-37.
15. Demographic Yearbook of Kazakhstan. Statistical compilation. Astana, Ministry of National Economy of the Republic of Kazakhstan: Committee on Statistics 2018; 2018.
16. Hutchinson K, Healy M, Crowley V, Louw M, Rochev Y: Verification of Abbott 25-OH-vitamin D assay on the architect system. *Practical laboratory medicine* 2017, 7:27-35.
17. Westgard JO, Miller WG, Allen K, Boone DJ, Caine P, Cooper G, Garber C, Greenberg N, Jain C, Linnet K: Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions: Approved Guideline: CLSI; 2006.
18. Bouillon R, Van Schoor NM, Gielen E, Boonen S, Mathieu C, Vanderschueren D, Lips P: Optimal vitamin D status: a critical analysis on the basis of evidence-based medicine. *J Clin Endocrinol Metab* 2013, 98(8):E1283-1304.
19. Halyk Finance. National Statistics Committee of the Ministry of National Economy (2017), "Kazakhstan is on the rise, Kazakhstanis are in recession", available at: https://inbusiness.kz/ru/news/kazahstanna-podeme-kazahstancy-v-recessii#gallery-2 (accessed 2 August 2019).
20. Barake M, Daher RT, Salti I, Cortas NK, Al-Shaar L, Habib RH, Fuleihan GE-H: 25-hydroxyvitamin D assay variations and impact on clinical decision making. *The Journal of Clinical Endocrinology & Metabolism* 2012, 97(3):835-843.
21. Carter G, Berry J, Gunter E, Jones G, Jones J, Makin H, Sufi S, Wheeler M: Proficiency testing of 25-hydroxyvitamin D (25-OHD) assays. *The Journal of steroid biochemistry and molecular biology* 2010, 121(1-2):176-179.
22. Cashman KD, Dowling KG, Škrabáková Z, Kiely M, Lamberg-Allardt C, Durazo-Arvizu RA, Sempos CT, Koskinen S, Lundqvist A, Sundvall J: Standardizing serum 25-hydroxyvitamin D data from four Nordic population samples using the Vitamin D Standardization Program protocols: Shedding new light on vitamin D status in Nordic individuals. *Scandinavian journal of clinical and laboratory investigation* 2015, 75(7):549-561.

23. Nugmanova Z, Patel N, Akhmetova GM, Kurmangalieva GS, Abdumananova MK, Akanov AA, Kovtunenko NG, McNutt LA: Relationship between vitamin D and human immunodeficiency virus (HIV) viral load among HIV-infected patients in Kazakhstan. *Journal of infection in developing countries* 2015, 9(11):1277-1283.
24. Algazinsmall a CT, Touir G, Pshembayevsmall a CS, Jetpisbayeva Z, Batpenova G: [The role of vitamin d in the development of psoriasis and acne]. *Georgian medical news* 2019(290):96-100.
25. Markabayeva A, Bauer S, Pivina L, Bjorklund G, Chirumbolo S, Kerimkulova A, Semenova Y, Belikhina T: Increased prevalence of essential hypertension in areas previously exposed to fallout due to nuclear weapons testing at the Semipalatinsk Test Site, Kazakhstan. *Environmental research* 2018, 167:129-135.
26. Dyussenova L, Pivina L, Semenova Y, Bjorklund G, Glushkova N, Chirumbolo S, Belikhina T: Associations between depression, anxiety and medication adherence among patients with arterial hypertension: Comparison between persons exposed and non-exposed to radiation from the Semipalatinsk Nuclear Test Site. *Journal of environmental radioactivity* 2018, 195:33-39.
27. Semenova Y, Pivina L, Manatova A, Bjorklund G, Glushkova N, Belikhina T, Dauletyarova M, Zhunussova T: Mental distress in the rural Kazakhstani population exposed and non-exposed to radiation from the Semipalatinsk Nuclear Test Site. *Journal of environmental radioactivity* 2019, 203:39-47.
28. Turgunova L, Laryushina Y, Turmukhambetova A, Koichubekov B, Sorokina M, Korshukov I: The Incidence of Depression among the Population of Central Kazakhstan and Its Relationship with Sociodemographic Characteristics. *Behavioural neurology* 2017, 2017:2584187.
29. Guide to Meteorological Instruments and Methods of Observation, vol. 8, Seventh edition edn: World Meteorological Organization; 2008.
30. Kazakhstan could become a PV solar energy powerhouse, available at: https://medium.com/@solar.dao/kazakhstan-could-become-a-pv-solar-energy-powerhouse-6f682a5efa07 (accessed 1 August 2019)
31. Ministry of Energy of the Republic of Kazakhstan Republican State Enterprise “Kazhydromet” Scientific Research Center: Annual bulletin of climate change monitoring in Kazakhstan: 2016. In. Astana; 2017: 53.
32. Wacker M, Holick MF: Sunlight and Vitamin D: A global perspective for health. *Dermato-endocrinology* 2013, 5(1):51-108.
33. Hearst MO, Himes JH, Johnson DE, Kroupina M, Syzdykova A, Aidjanov M, Sharmonov T: Growth, nutritional, and developmental status of young children living in orphanages in Kazakhstan. *Infant mental health journal* 2014, 35(2):94-101.
34. Schleicher RL, Sternberg MR, Looker AC, Yetley EA, Lacher DA, Sempos CT, Taylor CL, Durazo-Arvizu RA, Maw KL, Chaudhary-Webb M *et al*: National Estimates of Serum Total 25-Hydroxyvitamin D and Metabolite Concentrations Measured by Liquid Chromatography-Tandem Mass Spectrometry in the US Population during 2007-2010. *J Nutr* 2016, 146(5):1051-1061.
35. Janz T, Pearson C: Vitamin D blood levels of Canadians: Statistics Canada Ottawa (Canada); 2013.
36. Cashman KD, Dowling KG, Skrabakova Z, Gonzalez-Gross M, Valtuena J, De Henauw S, Moreno L, Damsgaard CT, Michaelsen KF, Molgaard C *et al*: Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr* 2016, 103(4):1033-1044.
37. Pludowski P, Ducki C, Konstantynowicz J, Jaworski M: Vitamin D status in Poland. *Pol Arch Med Wewn* 2016, 126(7-8):530-539.
38. Pivina L, Semenova Y, Dosa MD, Dauletyarova M, Bjorklund G: Iron Deficiency, Cognitive Functions, and Neurobehavioral Disorders in Children. *J Mol Neurosci* 2019, 68(1):1-10.

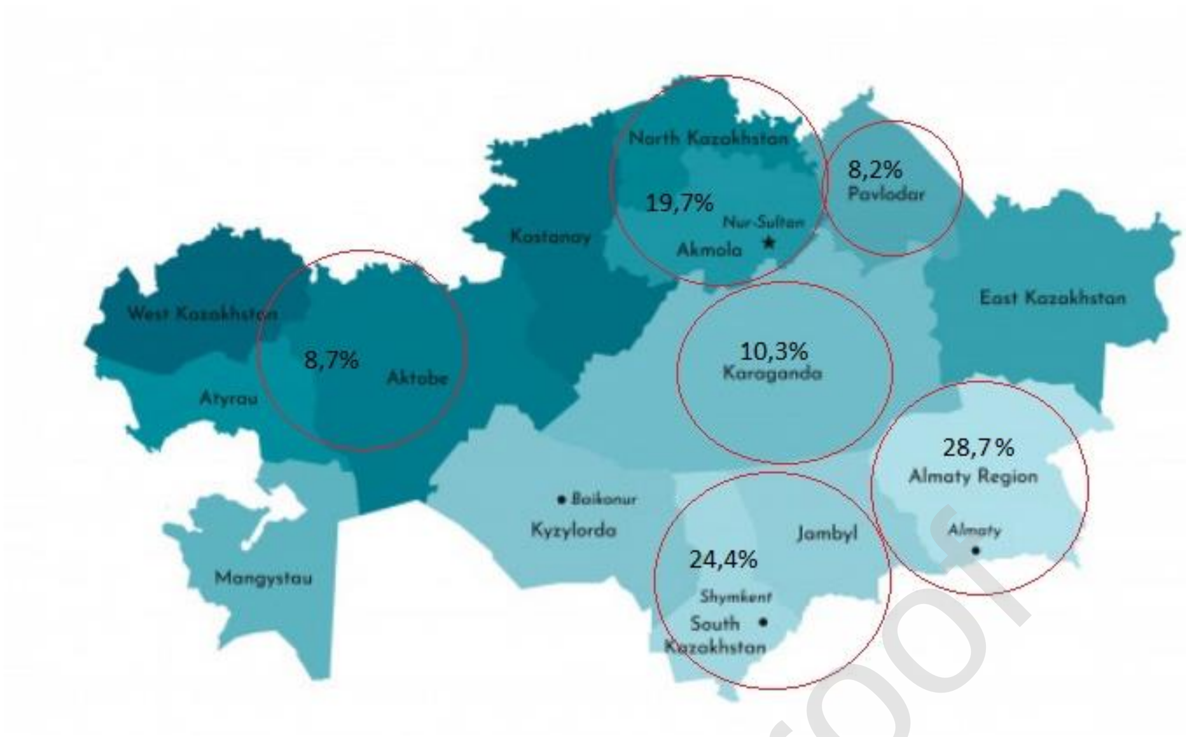

Figure 1. The Kazakhstan administrative map with shares of participants enrolled in the study (n=1347)

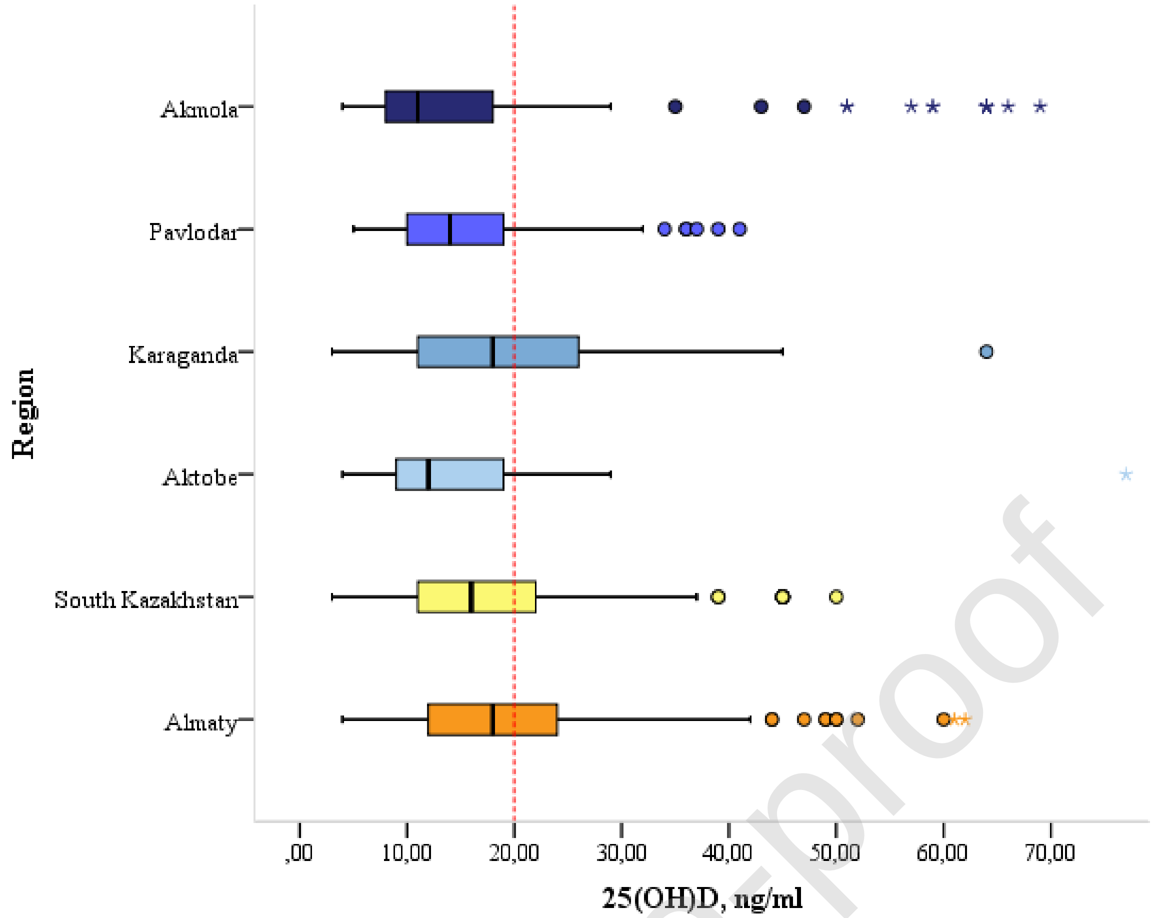

Figure 2. The median of 25(OH)D concentration in the study regions, Kazakhstan, (dash line is the lowest range of normal concentration = 20 ng/mL)