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Assessment of the association between sociodemographic characteristics and response to vitamin D supplementation using artificial neural network

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ABSTRACT

Introduction: Despite an agricultural country, India confronting malnutrition as a major public health challenge, where every second child is at risk of malnutrition. The nation ranking second in population with disproportionate rural and urban demography, further poor penetration of government assisted programs in remote, underserved areas fuelling the malnutrition in rural areas.
Methods: This cross-sectional study was conducted in Department of Community Medicine of Rohilkhand Medical College and Hospital. Total 465 schoolchildren in rural and urban areas of Bareilly district were screened for malnutrition and their socio-demographic profiles were studied.
Results: Overall, the prevalence of malnutrition in schoolchildren of Bareilly district was %40.2. Fraction contributed by urban and rural territories was %35.2 and %43, respectively. The prevalence of malnutrition was found higher in rural area as compared to urban area and the difference was statistically significant (P<0.001).
Conclusion: The study shows %43 prevalence of malnutrition in rural areas and under nutrition was the main cause of malnutrition attributed by poverty and illiteracy. However, urban areas reported %7.8 lower prevalence of malnutrition, but alarming trends of overweight and obesity %15.2.

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Introduction

Vitamin D (Vit D) is a steroid hormone that is produced in the skin through exposure to ultraviolet (UV)-induced isomerization of 7-dehydrocholesterol (7-DHC), and this is then converted to 25(OH)-vitamin D and 1,25(OH)-vitamin D (the active form), by two hydroxylation steps that occur in the liver and kidney, respectively (1). In recent decades, Vit D has been attracting increasing attention due to the important role of this vitamin in a wide spectrum of physiological pathways and multiple aspects of human health (1). It has been demonstrated that Vit D inade quacy

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directly related to unfavorable health conditions such as human malignancies, multiple sclerosis, hypertension, myopathy, infectious diseases, insulin-dependent diabetes, osteoporosis, osteopenia, asthma, as well as multiple psychiatric disorders i.e. depression and dementia (1-5).Serum 25-hydroxyvitamin D [25(OH)D] is the most extensively used and most sensitive index of Vit D status. Nearly one billion people across the world were estimated to have Vit D deficiency or insufficiency (serum Vit D levels <20 and <30 ng/ml, respectively) (6, 7).

Vit D requirements for health life fulfill through outdoor sun exposure about 20-30 min/day, or by use of Vit D food resources including natural animal origin foods i.e. fatty fish (salmon, sardines, herring, and mackerel) and oils derived from fish or synthetic sources i.e. fortified dairy products, and dietary supplements (8). Several sociodemographic parameters may be associated with low Vit D status such as advanced age (9), cultural factors (i.e. skin covering) (10, 11), native ancestry (12), low consuming of milk (13), higher skin pigmentation or black ethnicity (13-16) , over weight/obesity (14, 17), and lower education attainment (18). Low 25(OH)D can be improved by Vit D supplementation, to potential advantage for public health.

Although, the response to supplementation, regarding to the elevation in serum 25(OH)D concentrations, differs between persons. To best our knowledge, there is no comprehensive research which has evaluated appropriate Vit D intervention doses for various age groups across the world and current recommendations for supplemental Vit D are stand only on single particular health issue such as bone health and tumor; also, reports included in these reviews were not solely randomized controlled trials. Multiple parameters such as baseline 25(OH)D level, age, BMI, body fat mass, ethnicity, amount of fat and calcium in diet, genetics, estrogen use, latitude, season, medical comorbidities and taking medications as well as type, dose and duration of supplement has been found to may be affect magnitude of response to supplementation(19-24).

Data mining is applied in order to extract information from large amounts of data which integrated from numerous science fields. Because of the high heterogeneity and complexity of medical information, the analysis requires the AI based method to manipulate this information such as Artificial Neural Network (ANN). ANNs are one of the best data analysis methods that have been progressed to dominate restrictions of linear models(25).

ANN has demonstrated to be a superior predictive analytics compared to classical statistical approaches in various clinical settings such as primary association and risk factors of different health condition (26, 27).

To promote the public health issue, it is important to explore multiple variables together as certain combinations of deterministic parameters could be important for responsiveness to Vit D supplement. Moreover, knowledge on sociodemographic issues importance for 25(OH)D level could assist health advancing decisions in subgroups among young adults. To the best of our knowledge, this issue has not been addressed previously.

In this study, we probed the determinants of responsiveness to Vit D supplements in adolescent girls –sociodemographic and lifestyle factors– to shed light which factors are important for Vit D supplement recommendation by using ANN method.

Materials and methods

1.Study design

This prospective interventional study comprised adolescent girls (n=529) aged between 12-19 years old in spring 2017, as described previously (28, 29). In brief, all participants were asked to consume nine Vit D capsules containing 50000IU Vit D during nine weeks. All study procedures were approved by the Ethics Committee of our university. Informed consent was get from girls and their parents.

2.Anthropometric and biochemical measurements

Anthropometric variables were quantified and then body mass index (BMI) was calculated.Fasting blood specimens were collected early in morning at pre- and post-trial. Serum 25(OH)D levels was measured by an electrochemiluminescence (ECL) technology (Roche, Basel, Switzerland).

3.Family structure and socioeconomic conditions

The socioeconomic factors and family structure data were gathered by questionnaire which was previously approved in the Progress in the International Reading Literacy Study (PIRLS) for Iran (30).

Socio-economic data, including: the highest education levels were determined independently with 2 response options; 'No-College/University (lower than 12 years)' and 'College/University (higher than 12 years)' for maternal and 3 response options; 'basic (below 9 years)', 'intermediate (10 to 12 years)', or 'College/University (higher than 13 years)' for paternal. In addition, parent's occupation was assessed by querying parents to declare their profession through choosing one of the below response selections:

Mother's job: employee; housewife.

Father's job: worker; employee; tradesmen market; other.

4.Assessment of covariate

Physical activity was determined by a validated questionnaire and expressed as metabolic equivalents (METs) in hours/day (31). Exposure to smoke (passive smoking) status and sunscreen usage were also gathered.

5.Statistical analysis

The normality of data was determined using the Shapiro-Wilk tests. Descriptive statistics are including frequency or mean± standard deviation (SD). Kruskal-Wallis test or chi-square/Fischer's exact test was employed to compare the demographic, anthropometric and biochemical variables across the tertiles of elevation in serum 25(OH)D levels in response to supplementation.

5.1. ANN approach for predicting Vit D response to supplementation

ANN is a common technique of artificial intelligence which consists of nonlinear processing elements (named neurons) arranged in over interconnected layers in a configuration to emulate the human brain. The ANN model, when had one hidden layer with sufficient number of hidden neurons, can efficiently estimate any variables (32). Although, there are no general rules to discover optimal number of hidden neurons and transfer functions among layers (33). Our solution for predicting serum Vit D response to intervention was the feed-forward ANN with back-propagation as the training algorithm by recruiting SPSS software version 19 (SPSS Inc., Chicago, USA). In order to do that, we divided the data randomly into two disjointed subsets with the proportion 70% training and 30% testing set. Then, we will select optimal transfer function between following algorisms: hyperbolic tangent or sigmoid transfer function in hidden layers with 2 to 5 hidden neurons and linear, softmax, hyperbolic tangent or sigmoid transfer function in output layer. In second step, we will assess optimal transfer function with 2 to 50 hidden neurons and select sufficient number of hidden neurons for the problem we are dealing with. Response variable were calculated as follows: the difference between the concentrations of Vit D pre and post administration (Δ25(OH)D]. In this data, 33th and 66th percentile of the size of response were used for cut offs of response to supplementation which categorized as low (<19.9 ng/mL), moderate (19.9-34.6 ng/mL), and high (>34.6 ng/mL) Vit D response (34). After that, the ANN input values are: baseline Vit D, BMI, age, physical activity, passive smoker status, use of sun protective cream, parent's occupation and education, number of family members, roommate, parent death/divorce, and exclusive room. Subsequently, the sensitivity, specificity, as well as accuracy area under the ROC curve (AUC) were obtained for visualizing, organizing and selecting classifiers according to their performance in selected ANN architecture.

Results

In present study, 529 adolescent student girls aged between 12-19 years old who full data available had included. Significant differences were found between three tertile classifications of response to Vit D supplemental, regarding baseline circulating 25(OH)D, age, and mother's occupation (P<0.05; Table 1).

Table 1: Comparison of Participants' sociodemographic characteristics according to the Tertiles of magnitude of Response to Vitamin D groups

Variables		Response to supplementation			P value
		Firt Tertile (n=176) ≤19.9 ng/mL	Second Tertile (n=176) 19.9-34.6 ng/mL	Third Tertile (n=177) >34.6 ng/mL	
Basal 25(OH)D (ng/mL)		13.32±12.41	7.90±6.03	7.45±4.84	<0.001
Age (year)		14.97±1.59	14.46±1.53	14.56±1.62	0.007
Physical activiy(MET/h)		46.10±4.12	45.16±2.86	45.75±4.13	0.18
BMI(kg/m2)		21.21±4.03	21.73±4.57	20.62±3.94	0.06
sun screen use	Yes	81(35.1)	80(34.6)	70(30.3)	0.39
	No	95(31.9)	96(32.2)	107(35.9)	
Passive smoking	Yes	116(33.1)	117(33.3)	118(33.6)	0.99
	No	60(33.7)	59(33.15)	59(33.15)	
Father's occupation	Worker	66(33.3)	56(28.3)	76(38.4)	0.28
	Employee	33(40.2)	25(30.5)	24(29.3)	
	tradesmen market	30(30)	39(39)	31(31)	
	other	47(31.5)	56(37.6)	46(30.9)	

Mother's occupation	Housewife	154(32.7)	150(31.8)	167(35.5)	0.017
	Non-housewife	22(37.9)	26(44.8)	10(17.3)	
Father's education	<9 years	72(32.3)	71(31.8)	80(35.9)	0.47
	10 to 12 years	73(31.6)	81(35.1)	77(33.3)	
	College/University	31(41.3)	24(32)	20(26.7)	
Mother's education	Academic	50(40.7)	34(27.6)	39(31.7)	0.12
	Non-academic	126(31)	142(35)	138(34)	
Family members	2-4	72(31.3)	75(32.6)	83(36.1)	0.68
	4-7	99(35.5)	93(33.3)	87(31.2)	
	>8	5(25)	8(40)	7(35)	
Roommate	With parents	166(33.3)	166(33.3)	166(33.3)	0.97
	Without parents	10(32.3)	10(32.3)	11(35.4)	
Parent death/divorce	Yes	12(36.4)	10(30.3)	11(33.3)	0.91
	No	164(33)	166(33.5)	166(33.5)	
Exclusive room	Yes	93(33.6)	95(34.3)	89(32.1)	0.78
	No	83(32.9)	81(32.2)	88(34.9)	

* Data was shown as mean±SD or number (percent).

Using Kruskal Wallis Test or Chi-square test

Figure 1.A shows the detection percentages of ANNs for the identification of best transfer function in hidden and output layers separately. When hyperbolic tangent function connected input neurons to hidden neurons and sigmoid function connected hidden neurons to output neurons, the best performance was obtain for ANN algorithm with three hidden neurons (training correct detection=53%, testing correct detection=45%).

Figure1: A) The correct classification percentage of different ANN models in both training and testing phase for multiple transfer functions

When hidden neurons increased to 40, the correct detection using the selected algorithm increased to 57% in training set (Figure 1.B). Close correct detection in training and test sets also reveal non over fitting in ANNs algorithms (Figure 1). So, the best performance ANNs model had 40 hidden neurons with hyperbolic tangent and sigmoid functions in hidden and output layer respectively.

Figure1: B) The correct classification percentage of selected ANN transfer function models in both training and testing phase for different hidden neurons

As shown in Table 2, 103 of 176 participants with low response to Vit D supplementation were categorized correctly by perfect ANNs model (62% training, 51% test). This model also correctly detected 91 of 176 moderate and 90 of 177 high response adolescent girls by sociodemographic and lifestyle factors (Table 2). Furthermore, the specificity, sensitivity, and AUC values were 72%, 66%, 73.4% for low; 68%, 62%, 69% for moderate; and 62%, 62%, 68% for high responsiveness to vitamin D supplementation respectively (Figure 2).

Table2: Power of the demographical variables for the response to supplemental vitamin D based on triples threshold values in training and test groups separately

Actual outcome	Training set (n=370)			Testing set (n=159)			Total (n=529)		
	Low	**Moderate**	**High**	**Low**	**Moderate**	**High**	**Low**	**Moderate**	**High**
Low	76(62%)	19	28	27(51%)	10	16	103(59%)	29	44
Moderate	21	71(55%)	37	15	20(43%)	12	36	91(52%)	49
High	21	32	65(55%)	23	11	25 (42%)	44	43	90(51%)

Figure 2: Roc curve of the ANN model

According to the variable importance from selected ANN (Figure 3), baseline serum Vit D (28.1%), BMI (13.8%), physical activity (12.1%), and age (7.6%) are the top-4 determinants of changing Vit D levels. Between sociodemographic factors, mother's education (6.4%), father's occupation (5.8%), and mother's occupation (5.6%) are important predictive factors. However, other variables had lower than 4% importance in response to Vit D levels.

Figure 3: The variable importance obtained from the selected ANN

Discussions

This is a first study which has used data mining to find the potential effect of different personal, medical, environmental, sociodemographic and lifestyle factors, on the serum 25(OH)D level response to 9 week of oral supplementation with 5000 IU cholecalciferol/week. ANNs are suitable statistical tools to analyze data for the prediction of fussy events. ANNs have already been used for the characterization of the multiple unfavorable health events (35). Until now, no study has applied ANNs to forecast responsiveness to Vit D supplement.

Our important finding highlighted is a potential role of socioeconomic factors which were possibly related to increase serum Vit D value related to supplementation. Occupation and education of father's and mother's explained 21.7% of variation in 25(OH)D concentrations in response to supplement. In agree with us, in a cross-sectional study among Pakistani healthy women, risk of Vit D deficiency was independently related with illiteracy [odds ratio(OR)=4.0, 95 % CI: 1.03–15.5] and < 30 min sun exposure daily (OR=2.1, 95 % CI:1.1–4.2)(36).

Results from a study among 3127 healthy Indian schoolgirls revealed that socioeconomic and lifestyle-related parameters such as i.e. sun exposure and physical activity may be significantly involved in determining serum Vit D status of the children and adolescents girl (37). Naugler et al. performed a large study including 158,327 subjects to evaluate the association between socioeconomic strata and Vit D status. Results showed that age, gender, education, immigrant status, first nation and income were all impressively can predict status of Vit D (38). In multivariate analysis, several variables including low household income, lower child age, more hours spent children for television watching and lower playing outside was significantly correlated with Vit D deficiency (39).

In elderly population, those who lived lonely or reported property and riches below the normal range had 1.5 times more the prevalence of Vit deficiency. These older may use a lower variety of food intake, lower utilization of fish, are more probably to have an unhealthy eating habit and may have less income for a sun-holiday (40-43).

Our model suggested that that over 13.8% of the variance in 25(OH)D elevation in response to supplementation is attributed to the BMI. However, the relationship between BMI and 25(OH)D elevation after Vit D administration could be as a result of sequestration in adipose tissue (44). In one study on healthy volunteers, BMI in comparison with absolute body weight, was the stronger determinant of 25(OH)D. Compared to normal weight cases, overweight and obese subjects had decreased serum 25(OH)D levels on average 8.0 of ng/mL and 19.8 ng/mL, respectively. The authors recommend that Vit D supplementation should be 2-3 and 1.5 times more for obese and overweight persons compared to normal weight subjects, respectively (45).

Saliba and coworkers reported that the elevation in serum 25(OH)D in response to Vit D supplement was upper in normal-weight individuals versus obese cases. Interestingly, normal-weight subjects in comparison with obese cases were more probably to get serum 25(OH)D levels more than 30 ng/ml particularly at fewer basal serum 25(OH)D values (46). In experimental model, after 24 h exposure to UV radiation, the elevation in serum Vit D concentrations was 57% fewer in the obese compared to the non-obese cases (47).

Our suggestion is at decreased serum level of 25(OH)D, the adipose tissues are initially saturated with Vit D; so, a higher fraction of the supplemented Vit D will be moved to the adipose tissues in obese individuals with lower 25(OH)D concentrations. The serum 25(OH)D amounts are decreased in obese individuals, which could be attributed to lower Vit D consumption, lower sun exposure, degradation and storage of Vit D in adipose tissue, or easily that obese cases have an increased distribution volume for Vit D (48-52). Another important index which impacts on the variation in Vit D status post treatment was the baseline serum 25(OH)D in our model. Individuals with lower baseline 25(OH)D not only did not require more Vit D to reach an optimal Vit D level, but they really responded to a same dose with a higher alteration in serum 25(OH)D compared to individuals with upper baseline levels (53).

Interestingly, our model showed serum responsiveness to Vit D supplements are also influenced by physical activity (12.1%) and live in households with smokers (2.5%). Previously, it has been shown that the expanse of physical activity was a substantial determinative of Vit D level. Really, physical activity in outdoors leads to higher sun exposure. This fact is accepted that there are a direct relationship between exposure to sunlight with Vit D levels in adolescents (54, 55).

On the other hand, basal serum 25(OH)D level remarkably contributed to alteration in 25(OH)D in response to supplements (56, 57). Low Vit D concentrations may affect physical endurance. It has been reported that physical activity to be lessen through severe Vit D deficiency in all age group because of the substantial role of this vitamin in muscle function (58, 59). Valtueña et al. (60) recognized the interplays between Vit D and physical activity in two possible directions, for instance, sufficient Vit D levels upgrade bone health only in active children or physical activity promotes bone health in cases with Vit D sufficiency.

Tønnesen and co-researchers evaluated 700 cases and announced the relative risk (RR) for Vit D deficiency was elevated for men, obese cases, smokers and whose exercised weekly (RR=2.09, 95% CI: 1.5-2.9 ; RR=2.00, 95% CI: 1.3-3.1 ; RR= 1.3, 95%CI: 1.02-1.7, and RR=1.88, 95% CI: 1.2-2.9, respectively). The risk was reduced for cases who were attending for a Bachelor's degree (RR=0.40, 95%CI: 0.23-0.68) (61). Colao et al. announced that Vit D concentrations were markedly related with BMI (r=-0.43, p<0.0001), smoking (r=-0.24; p<0.0001), and exercise performance (r=0.79; p<0.0001). In multistep regression analysis, Vit D concentrations were perfect predicted via exercise performance, fewer smoking addiction, and lesser BMI (62).

Recently, there is evidence for a significant relationship between serum 25(OH)D and smoking (63-65). In one study, 25(OH)D levels was decreased to 4.2ng/dl in a smokers versus non-smokers in all-aged participants. Multinomial logistic regression model showed that a young smoker had 58% higher risk of Vit D deficiency than non-smokers (63).

But other by using mixed models reported that smoking was not related to Vit D deficiency (66) or connected with an elevated risk of Vit D deficiency only among females (64). It has been suggested that smoking leads to suppression of the Vit D-PTH system (67, 68), although, the exact mechanism by which smoking may act on Vit D status is still unclear. It is possible that hydroxyquinones of cigarette may affect liver function and contributed in elevating intracellular calcium. Also, an alteration in hepatic metabolism of 25(OH)D is possible because smokers face to increased hepatic degradation as showed via the elevation of estrogens degradation (68).

Hence, predominant response to Vit D supplements by more active individuals in our analysis is extremely interesting as proper Vit D supplement uses potentially superior benefit the active adolescents. This is the first investigation that describes sociodemographic factors related with the extent of response to Vit D supplementation among adolescent girls. The other strength of this wok were the use of a novel statistically method, ANN, for statistical analysis of our multivariate data. However, our population recruited only adolescents girls, so further research is need to confirm our results in different age groups, race and ethnicity.

Conclusions

In conclusion, among various sociodemographic factors which affect the increase in Vit D levels in response to supplementations, baseline serum Vit D level (28.1%), BMI (13.8%), physical activity level (12.1%), age (7.6%), mother's education (6.4%), father's occupation (5.8%), and mother's occupation (5.6%) were found to be important variables. This interventional study provides particular recommendations to get 25(OH)D targets in adolescents with severe Vit D deficiency, perhaps indicating that demanding a higher dose to obtain optimal Vit D levels in some individuals. More research is required to prove our findings and to clarify the basis of these relationships.

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences. All participants and their parents gave written informed consent to be interviewed, for the interviews to be audio recorded and used for research purposes and publication.

Competing interests

The authors have no conflict of interest to disclose.

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