Applied Mathematics, 2021, 12, 546-555
https://www.scirp.org/journal/am
ISSN Online: 2152-7393
ISSN Print: 2152-7385

Times Series Applied to Study Vitamin D Seasonality in Argentina

José Bavio[1], Carina Fernández[1], Patricia Fernández[2], Beatriz Marrón[1]

[1]Depto. de Matemática Universidad Nacional del Sur, Bahía Blanca, Buenos Aires, Argentina
[2]IACA Laboratiorios, Bahía Blanca, Buenos Aires, Argentina
Email: jmbavio@yahoo.com.ar, fercristy5@hotmail.com

How to cite this paper: Bavio, J., Fernández, C., Fernández, P. and Marrón, B. (2021) Times Series Applied to Study Vitamin D Seasonality in Argentina. *Applied Mathematics*, **12**, 546-555.
https://doi.org/10.4236/am.2021.127038

Received: April 23, 2021
Accepted: July 3, 2021
Published: July 6, 2021

Abstract

In this study, we analyze how vitamin D (VD) serum levels flow with latitude and throughout seasons of the year within a population sample over three years, taking into account that VD is mainly photosynthesized in the skin from sun exposure. Vitamin D levels have been measured in 80,763 patients during 2013, 2014, and 2015. To accomplish the objectives, we first perform some inference tests like two-way Analysis of Variance (ANOVA) followed by post-hoc tests. Secondly, we develop time series techniques including cross correlation calculations. Least than 10% of the sample had healthy VD levels, which should be a fact of public health major concern. The effect of the interaction between the two factors, zones and seasons, was proved by ANOVA. The mean values which are significantly different were determined by post hoc test. Furthermore, we find that mean serum VD levels, measured as 25-hydroxy-VD, follow a seasonal lag pattern of 9 weeks, a delay for minimum and maximum values after the respective equinoxes and daily sunlight duration. Reliable estimates of the population are provided in the present study, since one of the strengths is its huge sample size. We have quantitatively characterized the seasonality of serum vitamin D levels in the Argentine and the seasonal lag pattern has been determined for the study region.

Keywords

Vitamin D Status, Population Study, Time Series Correlation, Interaction Effects

1. Introduction

It has been known for decades that VD is involved in calcium homeostasis and metabolism, from its absorption in the intestine to bone remodeling. Nevertheless, osteopenia, osteoporosis [1] and sarcopenia [2] continue to grow as health disorders. No significant amounts of VD are found in food, and its main source is sun exposure on the skin. Although some foods are supplemented in Argentina, there have been no updates for years or in the area of international recommendations [3].

In recent years, many VD non-classic functions have been discovered [4]. It is known now that chronic VD deficiency increases the risk of infectious and autoimmune diseases, cancer, high blood pressure, hormonal, cardiovascular, skeletal, muscular, metabolic, and affective disorders, as well as autism [5], among others.

VD is photosynthesized in skin by sun exposure and is therefore fluctuating, as it depends on the individual, environmental and sociocultural factors, such as season of the year, latitude, cloudiness, smog, skin pigmentation, age, lifestyle: body mass index, clothing, indoors time, use of sunscreen, etc. [6].

Although there is great interest in studying the influence of VD on health, there is little information based on seasonality of VD serum levels. The cyclical nature of serum VD levels flows with B ultraviolet (UVB) sunlight exposure. However, there is little research on large samples that address detailed empirical data on when the population reaches the maximum and minimum serum 25-OH vitamin D levels throughout the year.

The above mentioned variables determine that the data of a nation cannot be applied to others so that motivated us to carry out this study specifically within our country. This research has been developed in years in which there was practically no medical VD supplementation.

We aimed to assess baseline serum levels of 25-OH vitamin D in the population sample, relate it to its location, evaluate differences and similarities between areas and seasons in order to provide estimates of optimal values of the delay between solar light hours available and the moment when maximum VD level is reached.

Vitamin D Levels

25-hydroxy-vitamin D is a biomarker that better reflects a person's VD status, measured in ng/mL [7].

According to the Endocrine Society recommendations [3], VD serum levels are stratified as follows:

- deficiency, below 20 ng/mL,
- insufficiency, between 20 and 30 ng/mL,
- optimal, above 30 ng/mL.

2. Subjects and Methods

Vitamin D levels have been measured in 80,763 patients during 2013, 2014, and 2015, as total 25-OH Vitamin (D2 + D3) by chemiluminescence, Liaison, Diasorin. It is worth mentioning that during these years people were hardly supplemented with VD in Argentina.

According to quality control standards, this analyte has allowable limits of performance (ALP) of plus or minus (±) 15%, as stated by the Royal College of Pathologists of Australasia (RCPA), Allowable Limits of Performance for Biochemistry [8]. Therefore we took an optimal serum vitamin D level of 40 ng/mL or more so that we are sure it is always preferably above 30 ng/mL, as recommended by the Endocrine Society.

Additional information collected: date, age, gender, residence location, and clinical history. The homogeneity of the sample was monitored and divided into groups of interest.

2.1. Definitions of the Variables

The variables and their categorization are presented below:

1) Gender: Male (M) and Female (F);

2) Season: Winter (I), Autumn (O), Spring (P) and Summer (V);

3) Age: the age of each individual has been categorized into the following groups, up to 13 years, from 13 to 20 years, from 20 to 40 years, from 40 to 60 years and older than 60 years;

4) Location: this variable has been categorized into four zones according with the corresponding south latitude value: Z_1 = more than 45˚ south latitude, Z_2 = between 45˚ and 40˚ south latitude, Z_3 = between 40˚ and 35˚ south latitude and Z_4 = Less than 35˚ south latitude. The geographical distribution of the zones can be seen in **Figure 1**.

2.2. Statistics and Data Analysis

Statistical analysis was performed using InfoStat [9]. Chi square test was used to compare the proportion of people with healthy level of Vitamin D, this is serum 25-(OH) D concentration of at least 40 ng/mL, separately in each variable. The result showed that there was no significant difference in this proportion between the different age groups; however there was a significant difference between genders, zones and seasons, $p < 0.001$ (**Table 1**).

A study was carried out to test the effect of the zone, the season and the interaction between these two factors using two-way ANOVA.

The two-way ANOVA was highly significant ($p < 0.0001$), that is, there is sufficient evidence to affirm that the mean value of VD is not the same in each combination of both factors. Furthermore, the interaction is highly significant ($p < 0.0001$), which means that the effect of the stations on the mean VD level is not the same for each zone, this can be seen in the graphs that are presented in **Figure 2** where some of the curves are not parallel and even more there are crosses between some profiles.

Bonferroni post hoc tests were used to test which mean values are significantly different and which are not. The results are shown in **Table 2**, same letter means no differences were found ($p > 0.05$).

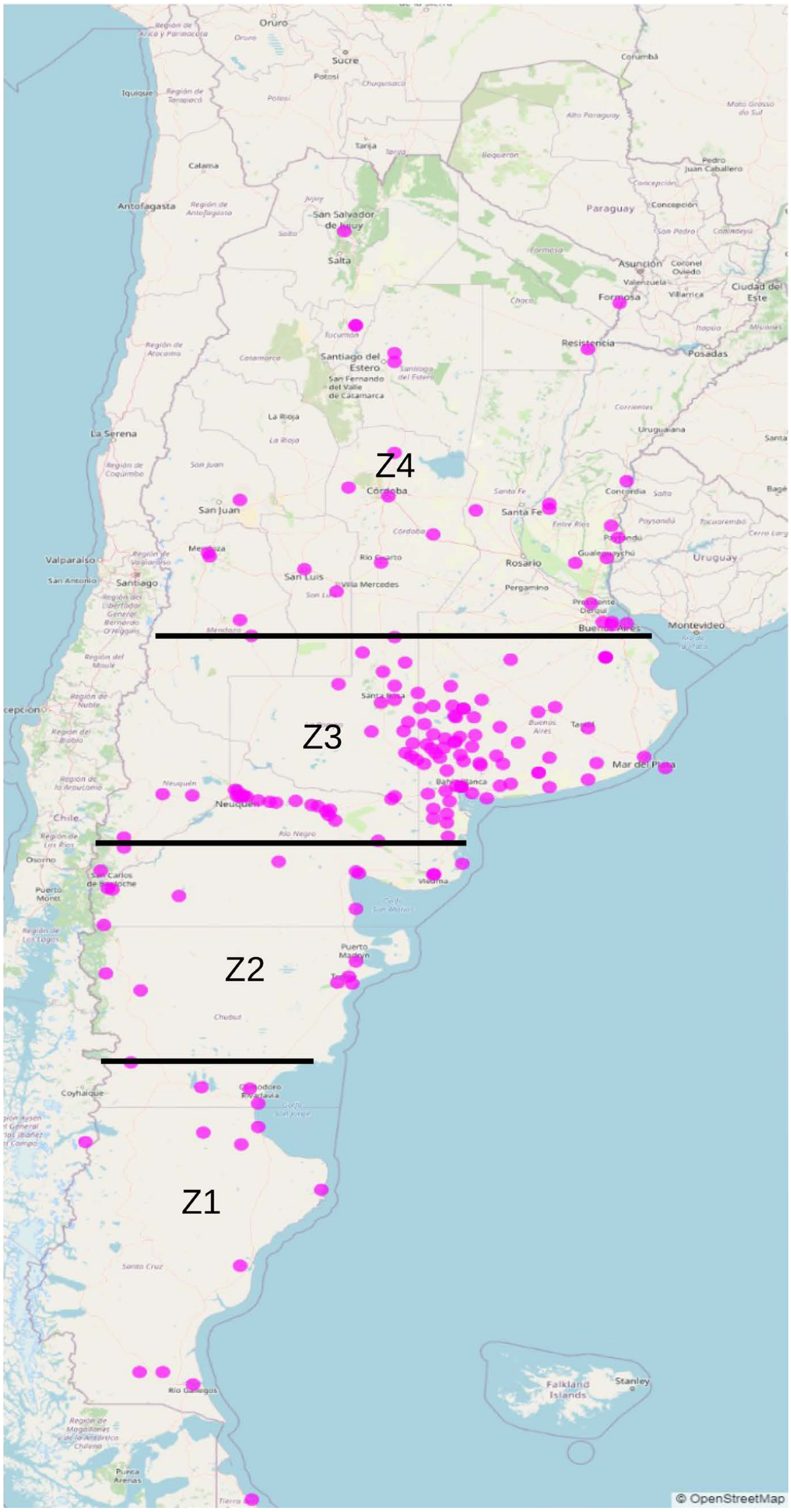
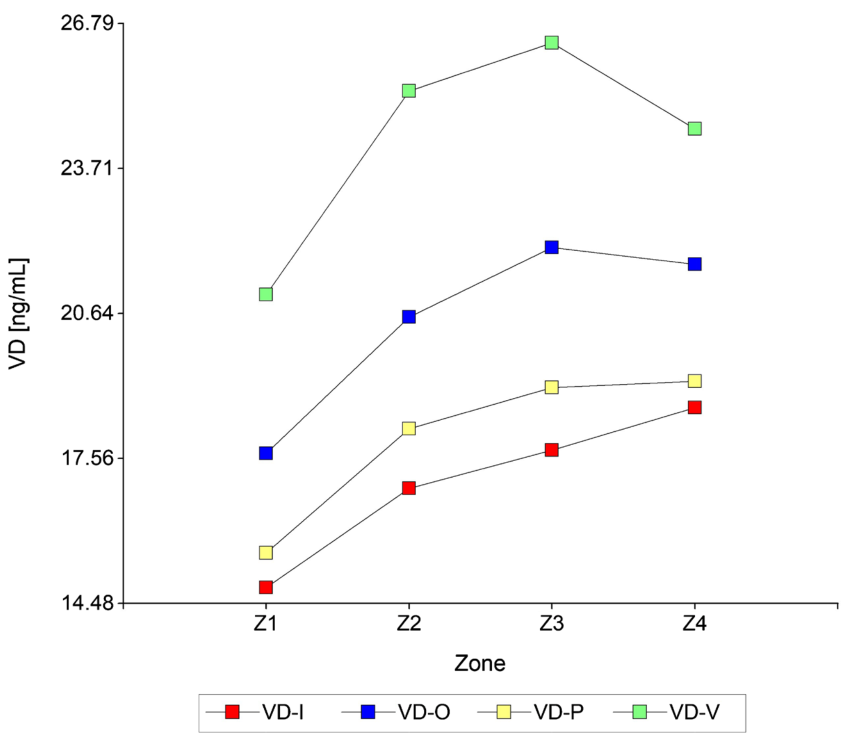


Figure 1. Zones and localities included.

Table 1. Number of individuals with healthy level of Vitamin D and their corresponding proportions.

	n	%	p
Gender			
Male (M)	366	3.38	
Female (F)	2939	4.20	<0.0001
Age			
(0; 13)	1310	5.32	
(13; 20)	50	8.14	
(20; 40)	334	5.01	
(40; 60)	805	5.75	
>60	606	4.77	0.3278
Season			
Winter (I)	472	2.14	
Autumn (O)	833	4.17	
Spring (P)	660	2.79	
Summer (V)	1340	8.85	<0.0001
Zone			
Z_1	341	2.18	
Z_2	733	4.19	
Z_3	1766	4.78	
Z_4	465	4.30	<0.0001



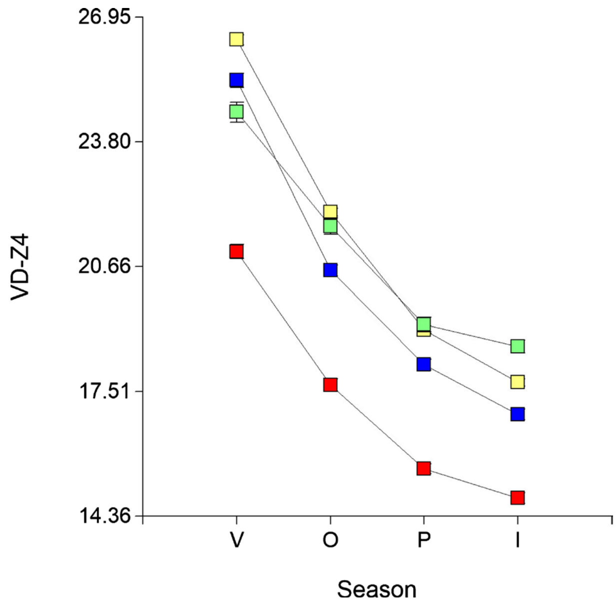


Figure 2. Significant effect difference was found on the interaction between Zone and Season.

Table 2. Bonferroni post hoc tests results, same letter $p > 0.05$.

	I	P	V	O
Z_1			A	B C
Z_2	B	C D F		A
Z_3	D	E		
Z_4	E F			

3. Time Series Analysis

Since vitamin D production is a function of skin exposure to ultraviolet (UVB) light, incident solar radiation can *a priori* be expected to be highly correlated with serum 25-(OH) D levels.

The results of the previous sections lead us to propose an analysis from the time series approach. To construct the series for the vitamin D data, we selected the dates that had at least one data and used interpolation for the other dates. **Figure 3** presents the graph of the series of quartiles Q_1, Q_2, Q_3 and the daily mean that showing the peaks and troughs.

Trend Decomposition and Correlation Analysis

Daily mean values time series is decomposed using Hodrick-Prescot (HP) filter into trend and high frequency components. This filter is a standard technique for separating long run trend in a data series from short run, high frequency fluctuations. It is a linear and symmetric filter that requires a parameter prior choice, λ, that modulates the softness of the tendency. Its proper choice depends on the length of the cycles to be extracted and the temporal periodicity of data.

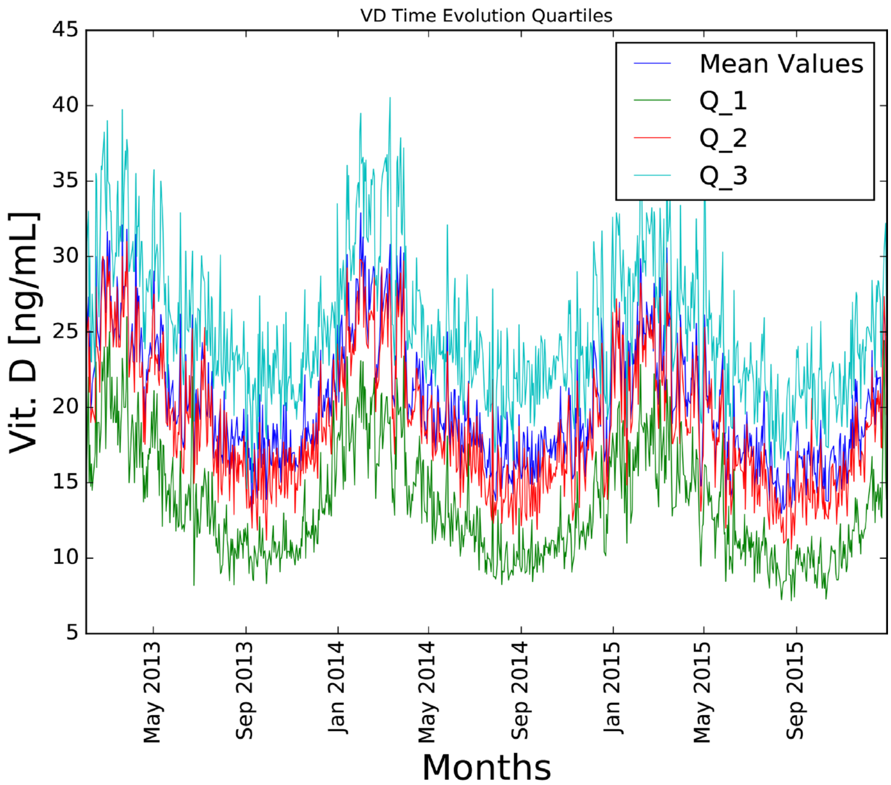


Figure 3. Series of Q_1, Q_2, Q_3 and mean values.

For data as used herein, the recommended value in the literature [10] is $\lambda = 14{,}400$.

Trend component shows maximum in summer and minimum in winter, which is an expected behavior since VD is synthesized by skin in presence of sunlight. Based on our knowledge on relation between VD and seasons, we perform correlation analysis between VD mean values and daylight duration according to [11], at 38 degrees south latitude, that is the middle center of zones in our data set.

It can also be appreciated as the number of hours of daily sun is forward, to the maximum and minimum of the VD average values. This is indicated by the vertical lines: the maximum corresponding to December 21 and the minimum to June 21 in south hemisphere. It is also shown, in dotted line, the delayed central tendency and how the maximum and minimum align with the amount of daylight hours, showed in **Figure 4**.

Correlation calculations provided a value of 9 weeks of the delayed interaction between the series. This value can be interpreted as the time for sun to affect VD in the organism, but it needs some careful considerations to derive this kind of conclusions.

Due to the great extension of the territory in which the analysis is carried out, and knowing that this can affect the number of hours of sunlight, we decided to fulfill the study dividing again into the already defined areas Z_1, Z_2, Z_3 and Z_4. The correlation analysis is performed between VD mean values and the daylight duration of the middle center of each zone. South latitudes used to calculate sun hours where, 50˚ for Z_1, 42.5˚ for Z_2, 37.5˚ for Z_3 and 32.5˚ for Z_4.

Although the delay value is not exactly the same in each zone, 9 weeks for Z_1, 7 weeks for Z_2, 8 weeks for Z_3 and 9 weeks for Z_4, the difference between them was relatively small to the time lapse spanned. The delayed central tendency for each zone and the alignment with the maximum and minimum of the number of daylight hours is shown in **Figure 5**.

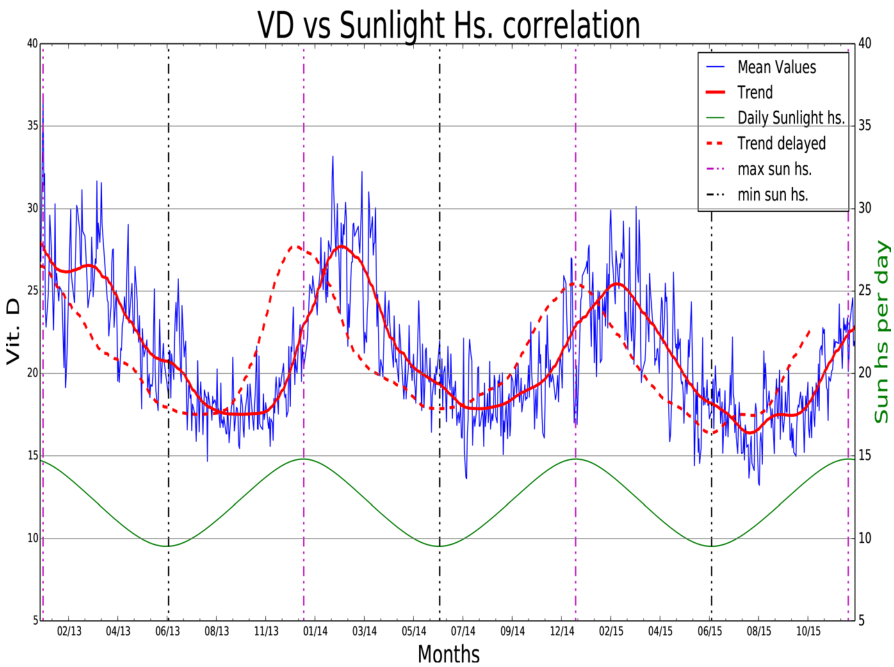


Figure 4. Trend and cyclical components. Left axis: level of VD; Right axis: sun hours per day.

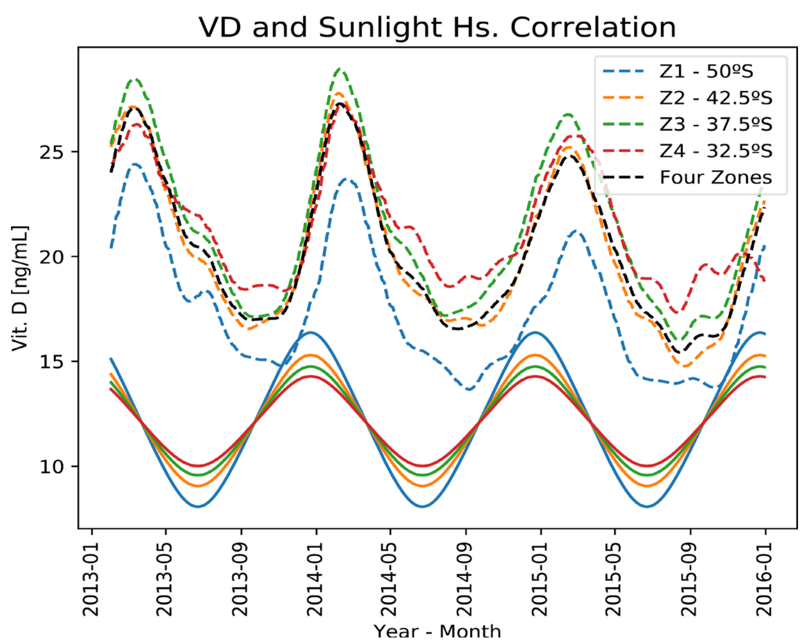


Figure 5. Trend and cyclical components. Each color represents a zone.

4. Conclusions

The strength of this study lies in the large sample size and includes the potential to generalize the results to the target Argentine population, by recruiting people from throughout the country considering that during the years of the study, hardly supplemented people with VD in the country. In addition, serum VD values were all measured using a single laboratory, which minimizes methodological differences on a single analytic platform at the same laboratory. On the other hand, a weakness that could be considered in the study is held by voluntary sampling, but despite that, the population proportions remained appropriate in each zone.

The study describes prevalence of vitamin D inadequacy in Argentinian population pointing out that over 90% of the population don't meet healthy VD levels. Going deeper in this analysis we carried out homogeneity tests on the proportion of individuals with healthy levels of Vitamin D. The result showed that there was no significant difference in this proportion between the different age groups; however there was significant difference between genders, zones and seasons of the year.

To prove the effect of the interaction between the two factors, zones and seasons, a two-way ANOVA followed by post-hoc tests was carried out. The most relevant results suggest that the variable studied has a similar behavior in Z_2 in winter (autumn) and Z_1 in autumn (summer); and in Z_4 (Z_3) in winter and Z_3 (Z_2) in spring. This means that areas of similar behavior could be medically treated or advised in a similar way.

With regard to the analysis of the time series, the peaks and troughs of serum VD levels follow a lag pattern of the 9-week seasons, reflecting the gradual increase of the mean levels of vitamin D in the population, during the months of greatest impact of sunlight, and the gradual decrease in the months of least impact. This result would make it possible to determine a protocol for VD supplementation.

In summary, we have quantitatively characterized the seasonality of serum vitamin D levels in the Argentine. In terms of cyclicality, these results could be applicable to all temperate populations in the southern hemisphere. However, differences in diet, the use of supplements, and sociocultural factors, have the skills to make it difficult to generalize to other countries.

Acknowledgements

The authors thank IACA Laboratory for providing data sets used for the current study. This work was partially supported by Universidad Nacional del Sur grant PGI 24/L112.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Joo, N.-S., Dawson-Hughes, B., Kim, Y., Oh, K. and Yeum, K. (2013) Impact of Calcium and Vitamin D Insufficiencies on Serum Parathyroid Hormone and Bone Mineral Density: Analysis of the Fourth and Fifth Korea National Health and Nutrition Examination Survey (KNHANES IV-3, 2009 and KNHANES V-1, 2010). *Journal of Bone and Mineral Research*: *The Official Journal of the American Society for Bone and Mineral Research*, **28**, 764-770. https://doi.org/10.1002/jbmr.1790

[2] NHANES Survey (2013) Centers for Disease Control and Prevention US Government. http://www.cdc.gov/nchs/nhanes/nh3data.html

[3] Holick, M., *et al.* (2011) Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology & Metabolism, **96**, 1911-1930. https://doi.org/10.1210/jc.2011-0385

[4] Hollis, B.W., Wagner, C.L., Howard, C.R., Ebeling, M., Shary, J.R., Smith, P.G., Taylor, S.N., Morella, K., Lawrence, R.A. and Hulsey, T.C. (2015) Maternal versus Infant Vitamin D Supplementation during Lactation: A Randomized Controlled Trial. *Pediatrics*, **136**, 625-634. https://doi.org/10.1542/peds.2015-1669

[5] Patrick, R.P. and Ames, B.N. (2014) Vitamin D Hormone Regulates Serotonin Synthesis. Part 1: Relevance for Autism. *FASEB Journal*: *Official Publication of the Federation of American Societies for Experimental Biology*, **28**, 2398-2413. https://doi.org/10.1096/fj.13-246546

[6] Wacker, M. and Holick, M.F. (2013) Sunlight and Vitamin D. A Global Perspective for Health. *Dermato Endocrinology*, **5**, 51-108. https://doi.org/10.4161/derm.24494

[7] Oleröd, G., Hultén, L.M., Hammarsten, O. and Klingberg, E. (2017) The Variation in Free 25-Hydroxy Vitamin D and Vitamin D-Binding Protein with Season and Vitamin D Status. *Endocrine Connections*, **6**, 111-120. https://doi.org/10.1530/EC-16-0078

[8] Australasia, R.C. (2014) Allowable Limits of Performance (alp). http://www.rcpaqap.com.au/docs/2014/chempath/ALP.pdf

[9] Di Rienzo, J., Casanoves, F., Balzarini, M., Gonzalez, L., Tablada, M. and Robledo, C. (2016) Grupo Infostat. http://www.infostat.com.ar

[10] Hodrick, R. and Prescott, E. (1997) Postwar U.S. Business Cycles: An Empirical Investigation. *Journal of Money*, *Credit*, *and Banking*, **29**, 1-16. https://doi.org/10.2307/2953682

[11] Forsythe, W., Rykiel, E., Stahl, R., Wu, H. and Schoolfield, R. (1995) A Model Comparison for Daylength as a Function of Latitude and Day of Year. *Ecological Modelling*, **80**, 87-95. https://doi.org/10.1016/0304-3800(94)00034-F