



## ORIGINAL RESEARCH

# Prevalence of Diminished Vitamin D and Association between Vitamin D-Levels and Morbidity by Acute Respiratory Infections (ARI) among Hospital Staff in Northern Bavaria during a Seasonal Flu Epidemic

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## Abstract

Although vitamin D is known to have an influence on the immune system, the impact of a low level on the susceptibility to ARI is not very clear. So the aim of this study was to investigate the prevalence of diminished vitamin D in adult workers and the relationship between vitamin D-levels and the morbidity of acute respiratory infections (ARI) during the influenza epidemic in the first quarter of 2018 (Q1/2018) in Germany. Included were 60 employees of a hospital in northern Bavaria.\*

**Methods:** Immediately after the flare-up of the above-mentioned flu epidemic, namely in the following month of April, a blood sample was taken from each of the 60 volunteers for the determination of vitamin D. At the same time, a survey was conducted on the affection by ARI and various personal characteristics. Examination of the association between vitamin D and morbidity by ARI was performed with stratified and multivariate analyses.

**Results and conclusions:** A majority of the study participants had vitamin D-values below recommended levels (70% below 30 ng/ml; 37% below 18 ng/ml in the month of April). However, their susceptibility to ARI was not significantly increased during the flu epidemic in Q1/2018.

Individuals with vitamin D below the recommended levels should take appropriate measures to increase it because of its general physiological function in human health. In view of various limitations of this study it seems desirable to further review the effect of vitamin D on morbidity by ARI, respectively to investigate below which level an undersupply could increase their risks.

\*The results of this study were already presented as a poster at the 22<sup>nd</sup> World Congress "Safety and Health at Work", which was postponed from 2020 to September 2021 due to the pandemic (P04-10 in the congress program). Because the question of an influence of vitamin D on the severity of viral diseases came more often in focus during the pandemic, we think this manuscript - despite of the studies limitations - may be of general public interest.

## Keywords

Acute respiratory infection (ARI), Influenza, Flu epidemic, Vitamin D, Low vitamin D, Inability to work

## Introduction

The question for the seasonal characteristic of influenza epidemic has long been in focus. As early as 1981 Hope-Simpson concluded from data that "epidemic influenza appears to follow each year a path that parallels that of maximum solar radiation, lagging six months behind" and assumed a "seasonal stimulus" in the human host causing this phenomenon [1]. In 2006 Cannel, et al. suggested vitamin D as the responsible "seasonal stimulus", as this vitamin has multiple effects on human immunity and it is mainly acquired through ultraviolet radiation on the skin. They could find a number of pieces of evidence from literature for this proposal, but not a real empirical proof and not enough



**Citation:** Holbach M, Seese B (2022) Prevalence of Diminished Vitamin D and Association between Vitamin D-Levels and Morbidity by Acute Respiratory Infections (ARI) among Hospital Staff in Northern Bavaria during a Seasonal Flu Epidemic. J Infect Dis Epidemiol 8:256. doi.org/10.23937/2474-3658/1510256

**Accepted:** April 13, 2022; **Published:** April 15, 2022

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evidence to recommend vitamin D for the prevention or treatment of viral respiratory infections [2].

A Few years later, a team from Norway succeeded in demonstrating a seasonally inverse relationship between the intensity of solar irradiation and influenza-related illnesses and deaths in the general population, for which they cited vitamin D as a possible explanation, but also without real evidence for this [3].

A Japanese group sought clarification through the effects of vitamin D supplementation: In a randomized, double-blind study a lower incidence of influenza A infections was observed in school children who took vitamin D supplements during an influenza epidemic (in comparison to a placebo group). However, this has not been confirmed for influenza B; and for influenza A in a later repeated study of the same type on students only at the beginning, not in the further course of an influenza epidemic [4,5].

A meta-analysis by Martineau, et al. in 2019 (including 25 placebo-controlled double-blind studies) provided strong indication that vitamin D supplementation could protect against ARI. But significant protective effectiveness (measured by the rate of those who had undergone an ARI during the respective observation period) was only seen in those groups with very low vitamin D (below 25 nmol/l resp. 10 ng/ml: OR 0.58, 95% CI: 0.40-0.82;  $p = 0.002$ ), whereas in vitamin D levels above 10 ng/ml, it was just tended to be found (OR 0.89, 95% CI: 0.77-1.04;  $p = 0.15$ ). There were also relevant differences in the mentioned rate between the different age groups: Children or adolescents (aged 1 to 16 years) could be protected from ARI by the administration of vitamin D (OR 0.60, 95% CI: 0.46-0.77;  $p < 0.001$ ), while this was hardly the case for people aged 16 to 65 years (OR 0.93 95% CI: 0.79-1.10;  $p = 0.41$ ) [6]. - Doubts and controversies about the possible role of vitamin D in influenza prevention also resulted in a further literature review, by Gruber-Bzura in 2018 [7].

In summary, it remains unclear whether (adult) people have an increased risk of ARI when their vitamin D level is (moderately) reduced. Therefore, we determined the vitamin D supply in the staff of a north Bavarian clinic shortly after that relatively severe influenza epidemic that hit Germany in the first quarter of 2018 and examined whether there was a connection between low vitamin D levels and the occurrence of ARI during this epidemic.

## Methods

Immediately after the influenza epidemic in Germany in the first quarter of 2018 (Q1/2018) flattened out\*, a correlation study (target factor retrospectively determined) was carried out (particular ethical requirements not recognizable).

During the following month of April, to all employees of a northern Bavarian clinic was offered a determination

of vitamin D by blood test. This was combined with an anonymous survey (by a questionnaire, submission before the vitamin D value became known) about acute respiratory illnesses (ARI) during the time from January first to end of March 2018) and the resulting days with inability to work as well as various personal characteristics with possible influence on the disposition of ARI (in detail: Age, sex, current and previous vaccinations against influenza, smoking behavior). It was explicitly asked for the *subjective* inability to work as a result of an ARI, this means whether and on how many days, according to their own assessment, an inability to work had existed during the epidemic (irrespective of whether this was the case on working days or on days off or whether it had been certified by a doctor; (further explanation about that parameter in [8]).

In order to limit the influence of ingested preparations with vitamin D (medicines or dietary supplements) as far as possible on the analysis result, a 3-week relinquishment for such preparations was a condition for participation.

The blood samples respective the separated sera were frozen until the concentration of 25-hydroxyvitamin D (1,25- (OH) 2-D3) determined, this with a measuring range of 3 to 70 ng/ml.

The influence of vitamin D on the incidence of ARI during the defined period of time was carried out by stratification in 3 ranges, so determined that the number of persons contained in each segment was about the same ( $n = 18$  to 22, Table 1). In addition multivariate regression models were developed to adjust the effect of age and received vaccinations against influenza. The respective target values were: the indication of whether an ARI had been undergone during the epidemic and whether this had led to a (subjective) inability to work (Table 2).

\*According to the "Working Group on Influenza" (Arbeitsgemeinschaft Influenza am Robert Koch-Institut, Germany) this epidemic was predominantly caused by influenza B (about 68% of the influenza pathogens). It had started in the 52<sup>th</sup> calendar week (cw) 2017 and ended in the 14<sup>th</sup> cw 2018 with maximum in the 8<sup>th</sup> to 10<sup>th</sup> cw [9]. Thus, the period covered by our survey (to facilitate the reporting from January first to end of March 2018) was largely coincident with the epidemic.

## Results

60 people (52 women, 8 men, mean age: 44.8 years) participated in the study. The vitamin D values were on average 25.6 ng/ml (SD: 13.5 ng/ml). Of the 60 total 42 employees had a value below 30 ng/ml (according to expert opinion, a concentration above that is desirable [10]), 22 employees below 18 ng/ml and 3 below 10 ng/ml (lowest result: 7.4 ng/ml).

27 employees (45%) were affected at least once by an ARI in Q1/2018, of which 19 (32%) with a (subjective) inability to work.

**Table 1:** Acute respiratory illness (ARI) in the first quarter of 2018 and resulting inability to work among 60 employees of a North Bavarian clinic: In the total collective and stratified into 3 groups with different vitamin D levels.

	N	Age [years]		ARI in Q1/2018			Duration of ARI-related inability to work in Q1/2018	
		Mean*	SD	never	≥ 1	≥ 1 day not able to work	n	Median [days]
Total: Vitamin D 7 to > 70 [ng/ml]	60	44.8	12.7	33 (55%)	27 (45%)	19 (32%)	19	10
Vitamin D > 30	18	45.6	13.9	10 (56%)	8 (44%)	7 (39%)	7	6
Vitamin D 18 to 30	20	45.8	12.6	12 (60%)	8 (40%)	4 (20%)	4	12
Vitamin D < 18	22	43.2	12.2	11 (50%)	11 (50%)	8 (36%)	8	9

\*one value of > 70 ng/ml netted with 70 ng/ml

**Table 2:** Influence of vitamin D on morbidity with ARI and resulting (subjective) inability to work during the flu epidemic in Q1/2018 among 60 hospital employees in northern Bavaria.

Target variable:	ARI in Q1/2018 (one or more)				ARI-related inability to work (at least 1 day) in Q1/2018			
Logistic regression	Bivariate		multivariate*		Bivariate		multivariate*	
	OR (SD)	P	OR (SD)	P	OR (SD)	p	OR (SD)	p
Effect of Vitamin D (increase by 10 ng/ml)	0.92 (0.62-1.36)	0.6711	0.96 (0.64-1.44)	0.8489	1.03 (0.68-1.56)	0.8853	1.08 (0.71-1.65)	0.7156

\*with the variables "age" and "current influenza vaccine" in the model

In the group with vitamin D values below 18 ng/ml the percentage of those having reported an ARI (once or more often during the observation time) was slightly higher (far away from statistical significance) than of those with values above 30 ng/ml (50% vs. 44%, [Table 1](#)); whereas the rate of those having declared an inability to work (at least one day as a result of an ARI) was slightly lower (ditto) in the first group (36% vs. 39%). The median duration of this inability to work shows no continuous trend across the groups formed with 3 graded vitamin D ranges ([Table 1](#)).

With bivariate and multivariate regression analysis (the latter as a logistic regression with "age" and "current influenza vaccination" as independent variables), neither for "at least once an ARI" nor for "ARI-related inability to work" as the target value an (inverse) association with the vitamin D levels could be detected (OR (multivariate): 0.96 resp. 1.01, [Table 2](#)). Also with the addition of the variable "sex" or "cigarette smoking", the influence of vitamin D on the aforementioned morbidity features of ARI remained indifferent. This was also the case when, instead of the current vaccination status against influenza, the number of previous flu vaccines (estimated by the participants; 12 missing values at that) was included in each regression model.

## Discussion

Most of the study participants had vitamin D values below recommended levels (70% with values below 30 ng/ml [10]). This is certainly due to a low sunlight exposure of the clinic staff (as it is likely to be the case in

other indoor-related industries and a common feature of modern life). These individuals should increase their sun exposure or, as far as not possible or with the intention to avoid the risk of skin cancer, their vitamin D intake through diet/supplementation because of its general physiological functions in human health (e.g. on skeletal health).

Nevertheless, the incidence of ARI during the flu epidemic in Q1/2018 in Germany was not significantly increased in the people examined here. This applies both to the total ARI- incidence (including those with remaining ability to work) as well as exclusively to those with (subjective) inability to work as a result. Regarding the latter, a protective effect from a higher vitamin D was not even hinted (OR<sub>biv</sub>: 1.03, OR<sub>multiv</sub>: 1.08, each in relation to a 10 ng/ml higher level), while for the overall ARI-incidence such a very small effect may have been indicated (OR<sub>biv</sub>: 0.92, OR<sub>multiv</sub>: 0.96, reference as above), but far from statistical significance (p = 0.67 resp. 0.85, [Table 2](#)).

However, only a few persons of the collective (n = 3 or 5%) were in a vitamin D range below 10 ng/ml, for which there is a general consensus to qualify this as "deficient" [11] and for which in the meta-analysis of Martineau, et al. a (highly) significant protective effect against ARI was found through supplementation [6]. Taking also into account that the vitamin D levels here referred to the month of April and thus to a time when they are usually significantly lower (up to about 45% lower than in summer [12]), the findings obtained here do not contradict those of Martineau, et al. Whereas,

they point out that low levels of vitamin D *in the range found here* (25.6 ng/ml, SD 13.5 ng/ml, related to April) do not (yet) increase the risk for adults of getting affected by an ARI.

The validity of the statement just made is, however, limited due to some *methodological limitations* of this study. Since no prospective investigation was possible under the circumstances here (e.g. unpredictability of a flu epidemic on the one hand, uncertain transferability of pre-seasonally determined vitamin D values on the other), the sampling and questioning took place (immediately) after the end of the observed flu epidemic.

With this approach, a possible influence of influenza infections (or ARIs that have been through) on the vitamin D level must be taken into account. Such an impact on the results can hardly have been the case, however, since it is unlikely that such infections lead to elevated values, either through internal processes or with regard to the behavior of those affected.

The determination of the two target variables (ARI and resulting inability to work) was carried out retrospectively through a questionnaire based on subjective assessments of the study participants. This quite timely and in ignorance of the influence factor tested (vitamin D), but without the possibility to check the accuracy of this information. Therefore, distortions in memory, response behavior or (overlapping) confounding cannot be ruled out (e.g. a different health awareness could influence the assessment of the severity of an ARI or respective on its impact on the ability to work as well as on the vitamin D supply through sunlight or ingestion).

Although a 3-week waiting period for the intake of vitamin D was established as a prerequisite for participation in this study (see above), a disturbing influence cannot be completely ruled out (e.g. with regard to unrecognized preparations in which vitamin D is just mixed as an additive).

And finally, the relatively small collective and its restricted representativeness is to consider: all hospital employees, mostly women (87%) and everyone presumably with a special interest in knowing the vitamin D level. The generalizability of this study is limited accordingly.

## Conclusions

A high proportion of the adult employees examined here were found to have vitamin D levels below recommended limits (70% had not achieved values of 30 ng/ml). These individuals should take appropriate measures to increase their vitamin D because of its general physiological functions in human health.

However, it cannot be concluded from this study that low vitamin D in the spectrum found here (mean value: 25.6 ng/ml, SD: 13.5 ng/ml, based on the month of

April) increases the susceptibility for ARI or its severity (as resulting inability to work) during a flu epidemic, as it occurred in the first quarter of 2018 in Germany. In view of the restrictions mentioned, it nevertheless seems desirable to carry out further studies on the influence of vitamin D on the morbidity of ARI respective on the threshold values below which an undersupply could increase their risks.

## Acknowledgments

Many thanks to the laboratory staff of the "Thoraxzentrum" in Münnerstadt and of the "Bezirkskrankenhaus" in Lohr as well as to the staff member of the occupational medicine unit in Lohr for their support in taking samples, performing the analyzes and all the other helpful contributions.

## Conflict of Interest

The authors have no conflicts of interest to declare.

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