Influenza, solar radiation and vitamin D

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; TOMS, total ozone mapping spectrometer; UV, ultraviolet

The annual death numbers of influenza and pneumonia in Norway were studied for the time period 1980–2000. No direct relationships were found with the variations of the annual UVB fluences, probably due to the fact that these variations did not exceed 30%. However, there was a very pronounced seasonal variation of both influenza deaths and pneumonia deaths, the vast majority occurring during the winter. Vitamin D levels were also estimated from several publications. The data support the hypothesis that a high vitamin D level, as that found in the summer, acts in a protective manner with respect to influenza as well as pneumonia. The findings are discussed and compared with data from tropical and subtropical areas.

Introduction

Nearly all human diseases related to respiratory pathogens exhibit seasonal variations.[1,2] The reasons for the seasonality, however, are still not known. Among the poorly tested hypothesis are: Seasonality of low temperatures, of dry air, of crowding together indoor in the winter, travelling patterns, vacations, seasonality of ultraviolet (UV) radiation from the sun that might kill pathogens, circannual rhythms of hormones like the "dark hormone" melatonin, etc.[3] Additionally, the question of whether it is the host or the vira/bacteria that exhibit seasonality arises. In the present work we have compared the seasonality of deaths of influenza and pneumonia in Norway with those of vitamin D photosynthesis and vitamin D serum levels.

Results and Discussion

Figure 1 shows the seasonal variation of vitamin D formation in human skin calculated from the known, 1990–2000 average levels of UV as earlier described,[8] using the action spectrum of Galkin and Terenetskaya.[9] The small dip in the curve in June is related to the cloud cover, which is taken into account. In agreement with earlier work, the vitamin D level is maximal about one month after the time of maximal formation, which occurs close to midsummer. This is due to the fact that the vitamin D level is here determined as the concentration of 25-hydroxyvitamin D [25(OH)D or calcidiol] in serum and that the formation of this metabolite from previtamin D, via vitamin D (mainly in the liver), takes some time. The fact that many have their vacation in July may also play a role. The observed delay is in agreement with earlier findings[11-14] and has been discussed in these papers.

In fact, the lowest vitamin D level is found in February, and average levels as low as 25 nmol/l have been observed among women avoiding direct sun exposure.

In both periods studied (1980–1989 and 1990–1999, **Fig. 1**), the death rates are very small in the season when the vitamin D status is best. The agreement between the death numbers in the two periods is good. This argues, although only weakly, for the common assumption that the seasonal variation of influenza is host related rather than caused by differences in the viral strains from year to year. This is also in agreement with recent observations that the same virus strain seems to be present in the hosts over longer periods, two years or more, but leading to manifest disease only under favourable conditions, mainly related to host immune weakening.[1,15,16] One might expect variations in the immune system to play major roles. Vitamin D interacts with the immune system, essentially strengthening it, in several ways as reviewed elsewhere.[17-19] Other pathways of interaction, like via circannual rhythms, cannot yet be ruled out.[20] The preventive effect of vitamin D supplementation has been demonstrated also in intervention studies.[21] Furthermore, Ginde et al. found that the serum levels of vitamin D were inversely associated with upper respiratory tract infections,[22] and it seems that exposure to artificial UVB radiation has a protective effect.[23] We, therefore, propose that the seasonal variation of influenza death numbers is related to the seasonal variation of vitamin D status.

An argument against this proposal from our data might be that the influenza death rates start to increase almost two months after the vitamin D levels have reached their minimum (**Fig. 1**).

However, one should remember that our register gives time-points for death, not for disease initiation. A delay of weeks is quite likely. Similarly, the death numbers start to decrease several
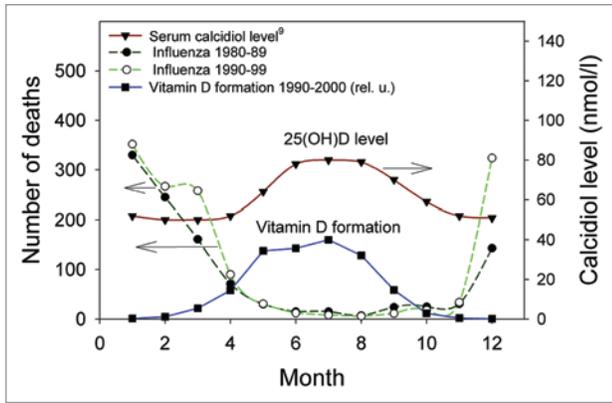
Figure 1. Seasonal variations of serum levels of vitamin D (▼) in the Nordic countries, given as averages from three reports in ref. 9. Photosynthesis of vitamin D for Southern Norway (■) is calculated by use of the action spectrum in ref. 7, UV measurements in Oslo and radiative transfer calculations using a cylinder model as described in the text. The results are presented in relative units (rel. u.). Influenza deaths in two periods (●, ○) in Norway are also given.

months before the vitamin D level starts to increase significantly. This is likely to be related to induction of better immunity. Thus, influenza pandemies, starting outside the classical winter influenza season, have a duration of not more than a few months, but also in the case of classical pandemies, like the Spanish flu, 1918–1919, there came a winter wave after the initial wave.[24] The first wave peaked in 1918, in October 19th in Baltimore, in October 26th in Augusta and in November 5th in San Francisco (an east–west wave), while the secondary wave came January 1919.

In future work other factors than vitamin D, essentially those mentioned in the introduction, should be taken into account. Out of these temperature and humidity may be the most important ones.[25-28]

Variation of summer UVB levels over the two decades, from 1980 to 2000, as shown in **Figure 2**, upper panel, are significant. For instance, from 1997 to 1998 there was a 20% decrease in the level. Annual numbers of influenza deaths do not reflect the variations of the UVB levels. This may be due to that the UVB variations are too small, notably in view of the fact that summer levels of vitamin D are not more than 30–50% higher than winter levels. Thus, a 20% decrease in summer UVB level would result in only a small overall decrease in vitamin D level, probably too small to influence the immunity next winter significantly.

Norway is localized from 58 to 70 degrees north, vitamin D being synthesized in skin exclusively in the summer months. It is, therefore, of interest to compare our data with data from tropical and subtropical regions. Generally, there is no distinct seasonal pattern in the tropics.[30-32] In Singapore small peaks were found in June–July and in November–January, coinciding with the winter in the Southern and northern hemisphere, respectively.[30] At latitudes between 20 and 30 degrees north, clear winter seasons of influenza are found.[15,33] This is at first sight surprising. However, we have calculated by the methods described above, that at 25 degrees north the rate of vitamin D
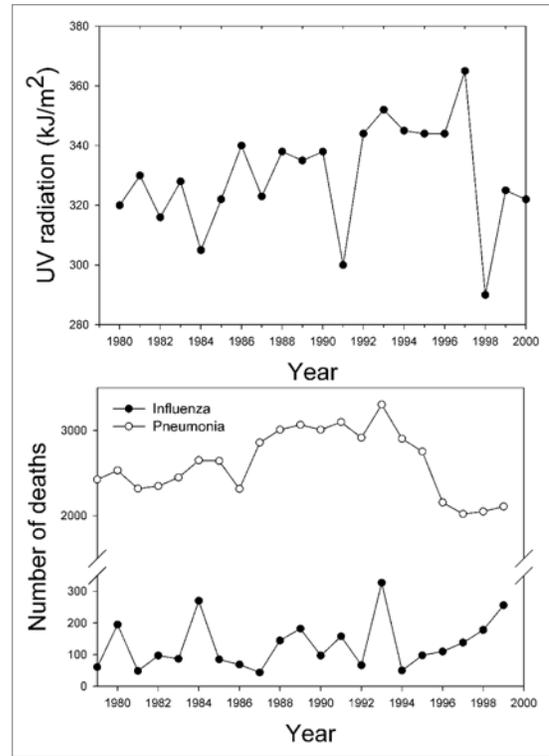

Figure 2. Upper: The UVB levels in Norway in the period 1980–2000.[29] In this case the UVB fluences were determined for a horizontal plane with the CIE erythema spectrum, which is UVB weighted and very close to the vitamin D spectrum used in the rest of this work. Lower: The average number of influenza and pneumonia deaths per year in Norway in the same period.

synthesis in human skin is about five times larger in late June than in late December. Sometimes secondary peaks are observed in June–August.[15,33] These peaks may be caused by other climatic factors than those directly related solar elevation.[34] Thus, cloud cover is likely to be involved since it will influence both humidity and UV penetration through the atmosphere. It seems that that many respiratory syncytial virus epidemics begin in coastal areas.[35]

Variations of the ambient UVB level have sometimes been proposed as factors related to influenza periods.[36-38] However, we have earlier shown that influence of variations of cloud cover on the annual UVB fluence is more than three times as large as that of variations of ozone levels.[39,40] Furthermore, during a sunspot cycle (about 11 years) the UVB fluence varies less than 1%.[39,41,42]

In conclusion, our data are in agreement with the assumption that the high numbers of winter influenza and pneumonia deaths in Norway are related to low vitamin D levels in this season.

Materials and Methods

Influenza and pneumonia deaths. The numbers of monthly influenza and pneumonia deaths were calculated by Prof. Øystein Kravdal from individual data provided by Statistics Norway. The numbers are averaged over the years 1980–1989 and 1990–1999.

It may be difficult know if the influenza deaths are caused directly by influenza or by secondary diseases.

Solar exposure and seasonal vitamin D formation. The main factors influencing the UV irradiances at ground level are solar zenith angle (variable with season, latitude and time of day), cloud and snow cover and the thickness of the ozone layer.[4]

In this study, the solar UV exposures were calculated using a radiative transfer model.[5,6] Total ozone amounts used in this model were measured by the Total Ozone Mapping Spectrometer (TOMS) satellite instruments. The daily cloud cover was derived from measured reflectivities by TOMS instruments and ground-based UV measurements in Oslo. A cylinder geometry of the human body was used. The arguments for this choice have been presented earlier.[7,8]

The results are presented as vitamin D forming UV doses. The efficiency spectrum for vitamin D production gives the relative effectiveness of solar radiation at different wavelengths in converting 7-dehydrocholesterol to previtamin D.[9] Briefly, an efficiency spectrum is calculated by multiplying the intensity of the solar radiation (wavelength by wavelength) with the action spectrum for the vitamin D production for the corresponding wavelength. The vitamin D action spectrum was taken from the publication of Galkin and Terenetskaya[9] which is similar to that measured by MacLaughlin et al. in ex vivo skin specimens.[10]

The vitamin D levels in different seasons are taken from an earlier publication[11] and are averages from three different experimental Nordic series described there.

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