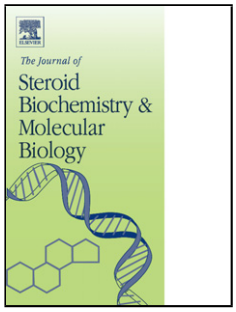

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Seasonal variations of U.S. mortality rates: Roles of solar ultraviolet-B doses, vitamin D, gene expression, and infections

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Highlights

- Death rates vary seasonally with lowest rates in summer.
- Circulatory and respiratory system diseases vary seasonally.
- The primary factor proposed is variations in solar UVB.
- Increased infections near the start of school raise rates.
- Vitamin D concentrations >36 ng/mL are recommended.

Abstract

Death rates in the U.S. show a pronounced seasonality. The broad seasonal variation shows about 25% higher death rates in winter than in summer with an additional few percent increase associated with the Christmas and New Year's holidays. A pronounced increase in death rates also starts in mid-September, shortly after the school year begins. The causes of death with large contributions to the observed seasonality include diseases of the circulatory system; the respiratory system; the digestive system; and endocrine, nutritional, and metabolic diseases. Researchers have identified several factors showing seasonal variation that could possibly explain the seasonal variations in mortality rate. These factors include seasonal variations in solar ultraviolet-B(UVB) doses and serum 25-hydroxyvitamin D [25(OH)D] concentrations, gene expression, ambient temperature and humidity, UVB effects on environmental pathogen load, environmental pollutants and allergens, and photoperiod (or length of day). The factors with the strongest support in this analysis are seasonal variations in solar UVB doses and 25(OH)D concentrations. In the U.S., population mean 25(OH)D concentrations range from 21 ng/mL in March to 28 ng/mL in August. Measures to ensure that all people had 25(OH)D concentrations >36 ng/mL year round would probably reduce death rates significantly.

Keywords

vitamin D; cardiovascular disease; mortality rate, season; respiratory tract infections; temperature; gene expression

1. Introduction

Death rates vary considerably by season, and even by day of the year. Between January 1, 1979, and December 31, 2004, the mean number of deaths/day in the U.S. ranged from approximately 5000 between days 200 and 240 to 6320 on Christmas Day (see Figure 1) [1].The authors of that study noted that the three days with highest death rates were Christmas, the day after Christmas, and New Year's Day. The most frequent causes of death associated with increases during Christmas week were diseases of the circulatory system; the respiratory system; the digestive system; and endocrine, nutritional, and metabolic diseases. The authors examined several possible explanations for the excess death rate for Christmas week and concluded that several factors probably contributed. However, no sole factor could be singled out, although they found evidence that hospital emergency departments on those days were overcrowded. From the data reported in their study, several other features are worth examining, such as the increase between days 20 and 80, the rise starting near day 240, and another rise starting near day 325, as well as

the longer-duration overall annual variation. Similar findings regarding the annual variations in overall mortality, and of the main diseases involved, have been reported in Europe [2], Japan [3], and Mediterranean countries [4]. A review of the seasonality of mortality in several countries found that most countries had minimum mortality rates in the second month after the solstice; however, Mediterranean countries had the lowest mortality rates in September [4]. A related study in Buenos Aires investigated monthly frequencies of diverse diseases that led to calls to the public emergency service and compared them with several meteorological variables and with season. They found no Christmas–New Year increases in calls; season rather than temperature was the apparent explanation for the winter peaks in calls [5].
Abbreviations: CDI, *C. difficile* infection; PM2.5, Particulate Matter, 2.5 micrometers or less;

Major causes of death for which seasonal variations are reported include acute cardiovascular "events"—myocardial infarction, dysrhythmias, heart failure and stroke, and various cancers. Mortality rates during hospital treatment for cardiovascular events, and for other common causes of death, may also vary by season of presentation. For some cancers, survival may vary with season of diagnosis.

Like other living organisms, humans have developed ways to protect themselves against adverse environmental factors experienced early in their evolution. Examples include extremes of temperature, periodic food shortages, and lack of sunshine as they migrated away from their equatorial birth place toward the poles, such as by having lighter skin pigmentation at higher latitudes [6]. However, as the pace of lifestyle change increases, evolutionary responses to changing environmental challenges are lagging, so that pollution, lack of exercise, unsuitable diets, extremes of food availability, and inadequate skin synthesis of vitamin D—especially severe in people of African ancestry who have migrated to temperate countries, or beyond—are not yet being countered. At the same time, responses developed for factors that threatened life early in our evolution can be inappropriate for current lifestyles. For example, increased food availability, and increasing fat and sugar intakes from increasingly used convenience foods mean that obesity is a rapidly escalating problem worldwide [7]. Disruptions of long-established living conditions that have led to well-established seasonal biological patterns affect human health, as they affect plant and animal welfare [8], and the combination of such factors complicates assessing how any single environmental factor influences specific health risks.

Despite these many and various findings, the objective of this study was to examine possible explanations for the variations in mortality reported with season. We conducted literature searches for papers reporting seasonality-related risk factors and for studies reporting the associations of such factors with specific mortality outcomes.

This paper discusses several factors identified as showing seasonal variation that might explain the seasonal variations in mortality rate:

1. Skin dosages of solar ultraviolet-B (UVB; either through its effect on vitamin D status, as assessed by serum 25-hydroxyvitamin D [25(OH)D] or through effects independent of any effect of vitamin D)
2. Gene expression
3. Ambient temperature and humidity

4. Effects of UVB independent of direct vitamin D–related effects on humans, that is, on environmental pathogen load (especially for gut and respiratory system)
5. Environmental pollutants and allergens
6. Photoperiod (day length)

2. Methods

Using pubmed.gov and scholar.google.com, we looked for papers reporting seasonal variations of mortality rates based on nationally reported mortality data (overall, and for the common respiratory and cardiovascular causes of death) and for papers considering how the above factors may be associated with mortality rates. We also sought papers that reported seasonal variations in deaths from digestive system infections, from hospital admissions with common disorders, from trauma, from surgery, and from admissions to intensive-care units.

3. Results of literature searches

3.1. Seasonal variations in solar UVB

Solar UVB doses vary with season as Earth orbits the Sun. Earth has an inclination of 23.5°; as it revolves about the Sun, the solar zenith angle varies depending on the phase of the orbit. The rates of synthesis of previtamin D_3 in the skin depends largely on the solar zenith angle. Engelsen has estimated the time required to make 400, 1000, and 4000 IU of vitamin D_3 for people with skin type 2 and 5 as a function of calendar day and fraction of skin area exposed [9]. For example, in Boston (42° N), to produce 1000 IU for skin type 2 would take 22 min with 12% of the skin area exposed, 10 min with 26% exposed, and 4 min with 58% exposed. In terms of seasonality, the time required varies sinusoidally. For a person with type 1 skin with face, neck, and hands exposed, the latitude where it takes only a few minutes to generate 400 IU of vitamin D_3 varies sinusoidally from 20° in December/January to 66° in June/July.

3.2. Seasonal variations in gene expression

The causes of seasonal variation in immune function have been considered, including photoperiod, or day length. However, this variable appears less likely to be important in humans than in hibernating animals, though melatonin production in humans can vary with day length [10]. A study reported in 2015 found widespread seasonal variations in gene expression for more than 4000 protein-coding mRNAs in white blood cells and adipose tissue [11]. In Germany, a study found that the anti-inflammatory circadian transcription factor *ARNTL* gene had a summer (June–August) peak 1.9 times higher than the winter (December–February) value. The summer value of the vitamin D receptor gene was 1.3 times higher than the winter value. Nine of the 16 circadian clock genes varied seasonally; the summer–winter ratios varied from 0.6 to 1.6. The summer–winter hormone receptor genes also varied from 0.6 to 1.5. In Gambia, the seasonality was linked to the rainy season, June–October. Both temperature and solar UVB doses are lower in winter in midlatitude countries and in the rainy season in Gambia. A similar study in the U.S. using data from the National Health and Nutrition Examination Survey (NHANES) found higher levels of neutrophils, white blood cells, and serum C-reactive protein in winter–spring than summer–fall [12]. Goldinger and colleagues also report seasonal variation in >600 healthy individuals in the Brisbane System Genetics study; seasonal variation in gene expression persisted after adjustment of the data for contemporaneous blood counts of relevant cell types,

for 74 transcripts for DNA repair and binding genes, and for 94 transcripts for genes with immune cell functions [13].

Possible drivers of the observed changes in gene expression, and in blood cell count variation, include day length, temperature, and UVB dose through production of vitamin D_3. The last of these is supported by a vitamin D_3 supplementation study in which supplementation with 2000 IU/d of vitamin D_3 for 2 months altered the expression of 291 genes in white blood cells by at least 1.5-foldcompared with 400 IU/d [14]. The genes modulated by vitamin D were linked to immune function, autoimmune diseases, cancer, and cardiovascular disease (CVD). In addition, as seen in supplementary Figure 2, standardized monthly values for 12 weather conditions [13], troughs for solar exposure, and solar UV preceded the trough for the cosine curve with a 12-month repeating cycle by about 1 month. This finding is consistent with 25(OH)D concentration lagging solar UVB exposure by 1–2 months [15].

Although day length is a possible driver of gene expression, the fact that the seasonality of gene expression was determined by the rainy season in Gambia, June–October, as opposed to December–February in the UK [11], argues against day length as the driver of seasonal variations of human gene expression.

Two findings are inconsistent with temperature having a major influence on gene expression, assuming that gene expression is an important factor for disease and death. One is that in Buenos Aires, season rather than meteorological conditions was more strongly correlated with temporal variations in rates of calls to the public emergency service [5]. The second is that CVD rates are higher in winter than in summer regardless of whether the country is extremely cold, as in Kazakhstan [16], or hot, as in Kuwait [17]. Thus, seasonal variations in solar UVB doses and/or 25(OH)D concentrations seem the most likely reason for seasonality of gene expression.

3.3. Respiratory tract infections

Risk of respiratory tract infections is highest in winter and lowest in summer. In 2006, Cannell and colleagues proposed that epidemic influenza was seasonal, largely because of seasonal variations in solar UVB doses and 25(OH)D concentrations. An analysis of a clinical trial of vitamin D supplementation of postmenopausal African-American women living on Long Island, New York, quickly offered experimental support for that hypothesis. Women taking 2000 IU/d of vitamin D_3 had significantly fewer colds or influenza episodes than those taking 800 IU/d or placebo [18]. A clinical trial with 1200 IU/d of vitamin D_3 of schoolchildren in Japan yielded more support. Children who had not taken vitamin D before enrollment—that is, those with baseline vitamin D deficiency—had a relative risk of developing type A influenza, after supplementation, of 0.36 (95% confidence interval [CI], 0.17–0.79; p=0.006) [19].

An observational study in Greenwich, Connecticut, involving 195 healthy adults, offers more evidence to support the seasonality of infectious diseases and likely protection by better vitamin D status. People with a mean monthly serum 25(OH)D concentration over 4–5months of the fall–winter period of >38 ng/mL had less than half the incidence rate of acute viral respiratory infections seen in those with lower concentrations [20].

An ecological study found that communities with higher solar UVB doses, both in summer and in winter, had significantly lower case-fatality rates during the pandemic influenza of 1918–1919

in the U.S. [21]. The mechanisms proposed included the induction of cathelicidin (or LL-37) synthesis by vitamin D. Cathelicidin's well-known antimicrobial and antiendotoxin properties would have protected against infection and reduced the severity of the inflammatory cytokine response to infection [22]. A study in South Korea found that a serum 25(OH)D concentration >20 ng/mL was associated with an adjusted odds ratio for mortality of 0.94 (95% CI, 0.90–0.99) for those who developed community-acquired pneumonia [23].

However, evidence indicates that other meteorological conditions also affect the seasonal variation in influenza rates. Three papers examined how temperature and humidity affect U.S. influenza rates. One found that influenza rates peak near the end of the year, when temperature and relative humidity are lowest [24]. In a study of the 2009 A/H1N1 pandemic influenza, the authors concluded, "These findings suggest that the timing of pandemic influenza outbreaks is controlled by a combination of absolute humidity conditions, levels of susceptibility, and changes in population-mixing and contact rates" [25]. Analysis of influenza incidence rates in the Health Professionals Follow-up Study found that the seasonal pattern of influenza incidence was better modeled using absolute humidity and the school calendar than seasonal variations in 25(OH)D concentrations [26]. However, other confounding factors are at work, such as how the influenza virus is spread by travel, and population mixing during the Christmas and New Year's holiday periods.

A study in Okayama City, Japan, for December 2006–April 2007 found that almost all influenza cases occurred in March [27]. A study in Egypt for 2006–2008 found that influenza A/H5N1 cases occurred around March, a month or two after the minimum temperatures [28]. In a study in Finland in 2005, influenza cases peaked in mid-February, following a period with average temperature in the range of 0° to –10°C [29]. The authors noted that when average temperature was lower, influenza rates decreased. These three studies from countries other than the U.S. seem to be more consistent with highest influenza rates near the time of lowest 25(OH)D concentration. Thus, although temperature and absolute humidity affect the risk of influenza, 25(OH)D concentrations seem to be more important.

3.4. Cardiovascular disease

CVD rates show a pronounced seasonality, with peak rates during January in the Northern Hemisphere and July in the Southern Hemisphere [30]. Scragg proposed in 1981 that the seasonality was likely to be linked to seasonal variations in solar UVB radiation and vitamin D production [31]. He later showed that risk of myocardial infarction was inversely correlated with baseline plasma 25(OH)D concentrations [32]. Observational studies strongly support the inverse correlation between 25(OH)D concentration and prospective incidence of CVD [33], [34].

A study from Sweden investigated the risk of venous thrombotic (blood clot) events for women. It found significant reductions in risk from use of sunbeds, sunbathing during winter vacations, sunbathing during summer, and sunbathing during vacations abroad [35]. A second study from the Melanoma in Southern Sweden cohort monitored 29,518 women for 20 years. Death from CVD was inversely related to sun exposure. The hazard ratio for avoiding sun exposure was 1.6 (95% CI, 1.3–2.0) in comparison with moderate sun exposure and 2.3 (95% CI, 1.8–3.1) in comparison with high exposure [36]. These two studies clearly identify sun exposure with prospective reduction in the risk of death from CVD.

UVA exposure vasodilates the arterial and arteriolar vasculature and lowers blood pressure [37],[38]. This effect may help explain the decrease in blood pressure with sunlight exposure [39], and since lower blood pressure protects against cardiovascular events [40], this may contribute to sunshine exposure–related reductions in death from CVD.

A clinical trial in England gave enrollees in the treatment arm 100,000 IU of vitamin D_3 every 4 months (equivalent to 830 IU/d) [41]. People in the treatment arm achieved mean 25(OH)D concentrations of 29.7 ng/mL, whereas those in the control arm achieved 21.4 ng/mL [42]. The age-adjusted relative risk for death from CVD was 0.84 (95% CI, 0.65–1.10;p=0.20). On the basis of the meta-analysis of all-cause mortality rate as a function of 25(OH)D concentration by Garland and colleagues [43], the hazard ratio for those two 25(OH)D concentrations would be about 0.86—close to that found in the early hypothesis-generating English study. The English study had two limitations: using a large vitamin D dose, which would let 25(OH)D concentrations vary between doses; and the few participants (101 case patients and 117 control subjects). However, even though the results of the English study were not significant, they are in line with the hypothesis that vitamin D supplementation reduces risk of death from CVD. In the RECORD trial (with treatment arms consisting of 800 IU/d of vitamin D, 1000 mg/d of calcium, both, or placebo), vitamin D supplementation significantly reduced the risk of cardiac failure but not of myocardial infarction or stroke [44]. However, that trial neither measured, nor used as an inclusion criterion, baseline 25(OH)D concentration. Thus, such trials are really addressing whether supplementing the general population with a modest amount of vitamin D has any benefit, but they are not evaluating the 25(OH)D concentration–health outcome relation efficiently, as proposed by Heaney [45].

Cold temperature also plays an important role in risk of CVD, and one risk factor related to temperature is blood pressure. A study from China analyzed that factor. Mean systolic blood pressure rose from 129 mmHg in summer to 142 mmHg in winter in several regions of China. However, it rose from 124 mmHg in summer to 135 mmHg in October but then decreased to 131 mmHg in January/February in Harbin, where 94% of the population had central heating [46]. That paper also reported a direct, linear relationship between systolic blood pressure and the hazard ratio for CVD mortality rate. Another study from Hong Kong found that emergency CVD hospitalizations increased significantly within 21 days of both moderate and extreme cold events [40]. A study in Boston found that a 5°C decrease in ambient temperature was associated with a 9% (95% CI, 1%–18%) increase in risk of stroke within the next 2 days, independent of season [47]. A study in Kazakhstan also found significant variations in CVD mortality rates with respect to temperature [16], and the minimum temperature in Kazakhstan during the study period was –10.3°C. On the other hand, CVD rates show a strong seasonality in Kuwait, with rates in January 40% higher than in summer [17]—though Kuwait is a very warm country. The findings from these two countries indicate that absolute temperature does not determine CVD mortality rates, though cold conditions are associated with higher mortality rates than undue heat. In a study of 540,450 person-years with 1719 vascular deaths, the HR for cold-related CVD mortality was 1.16 (95% CI, 1.03–1.29] without any increases in stroke risk. In addition, warmer ambient temperature during gestation was associated with increases in cold-related ischemic heart disease-, but not stroke-related, mortality (HR = 1.16 [95% CI, 1.03–1.09]) in a 1915–2002 Swedish cohort in Uppsala, where daily ambient temperature readings were available for that

period [48].The mechanisms for cold-related increases in CVD mortality are mainly those that increase the risk of intravascular clotting [49].

Atmospheric pollution also increases CVD mortality rates. An analysis of 4.5 million deaths in 75 U.S. cities from 2000 to 2006 found that a 10-μg/m^3 increase in PM2.5 (particulate matter with a mean diameter <2.5 μm) was associated with about a 1% increase in CVD mortality rates [50]. However, the seasonality of these deaths depends on factors such as meteorology (height of the inversion layer) and source of the pollutants. For example, increased deaths related to PM2.5 were associated with warm-season secondary aerosols and traffic, whereas in Seattle, increased deaths were most closely associated with cold season traffic and other combustion sources such as residual oil and wood burning [51].

3.5. Endocrine, nutritional, and metabolic diseases

Reasonable evidence indicates that vitamin D reduces risk of death from metabolic syndrome–related diseases.

Diabetes mellitus (DM) is a classic endocrinological condition where vascular and nonvascular complications impose a huge burden of morbidity and mortality from the disease on people with both type 1 (T1DM) and T2DM. Although causality for T2DM remains uncertain, statistically significant independent and inverse associations are evident between 25(OH)D status and both vascular and nonvascular mortality [52]. Furthermore, vitamin D status is negatively related to all-cause mortality prospectively for men with T2DM,whereas parathyroid hormone concentration is directly related to all-cause mortality for women with T2DM [53].

Diabetic patients are generally more prone to suffer from infections, including upper respiratory tract infections, than nondiabetics. Severe outcomes of influenza are associated with comorbidities including DM [54]. Also, West Virginia Medicare beneficiaries with DM who do not have prior claims for influenza vaccination had significantly increased risk of mortality [55]. Also, diabetics vaccinated against influenza had significantly reduced mortality compared with nonvaccinated diabetics [56]. Severe influenza seasons are reported following warmer-than-average winters; that is, low temperature mitigates the severity of influenza [57]. Thus, one can speculate that DM, together with higher ambient temperature, are risk factors for severe influenza and are associated with higher mortality.

Serum 25(OH)D concentration <15 ng/mL was associated with increased risk of death for people with non–dialysis-dependent chronic kidney disease in Ohio [58]. Similarly, hypovitaminosis D in patients suffering from diabetic nephropathy also is associated with increased all-cause mortality [59]. Also, low serum 25(OH)D concentrations have been implicated in allowing increased renin–angiotensin system activity, with renal disease progression [60]. Vitamin D blocks renin secretion [61] and reduces hyperglycemia-induced RAS overactivity in, for example, pancreatic islets [62], offering a relevant protective mechanism for reduction of diabetic tissue damage and in renal disease progression [63].

Vitamin D–replete patients with metabolic syndrome in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study had a significantly reduced all-cause cardiovascular disease mortality compared with their vitamin D–deficient counterparts. Furthermore, a

significant reduction in sudden deaths, and in deaths from congestive heart failure, was observed (i.e., in cardiovascular disease mortality) in those with optimal vitamin D status. Also, these reductions in mortality were dose-dependent for each specific cause measured [64]. The German Diabetes and Dialysis Study reported that their patients with severe vitamin D deficiency had a threefold-higher risk of sudden cardiac death than those with sufficient 25(OH)D concentrations [65].

3.6. Diseases of the digestive system

Clostridium difficile and norovirus are the top two leading causes of gastroenteritis-associated mortality in the U.S., with *C. difficile* largely accounting for the increasing trend in deaths [66].

The seasonality of the common infective digestive system diseases is largely determined by the bacterial and viral content of the water and food consumed. *C. difficile* infection (CDI) rate peaks in the Northern Hemisphere in spring, with a trough in summer/fall [67]. Norwalk virus (norovirus) and rotavirus infection rates both peak in winter in the U.S. [68].

A study in Turkey found that 70 patients with rotaviral diarrhea had a mean 25(OH)D concentration of 14.6 ± 8.7 ng/mL, whereas 67 matched patients without rotaviral infection had a mean 25(OH)D concentration of 29.1±6.5 ng/mL [69]. CDI rates are inversely related to 25(OH)D concentration [70], and prehospital 25(OH)D concentrations were inversely related to in-hospital CDI rates [71].

On the other hand, it appears that using UVB radiation to kill waterborne viruses may also play an important role in the seasonality of norovirus infections. Indeed, UV radiation is widely used to kill norovirus in shellfish in water [72] and can be used to reduce norovirus contamination in oyster sea farms [73].

Thus, it appears that serum 25(OH)D concentration has an important role in determining the severity of clinical illness in common gut infections, but that UVB radiation may also have an important role in reducing the risk of digestive system infective disease, directly, by inactivating viruses and perhaps killing bacteria.

3.7. Cancer

Cancer shows little seasonal variation in incidence or mortality rates, since the progression from initiation to death is generally a long, slow process. One exception is breast cancer, for which diagnosis rates are higher in spring and fall [74]. Several types of cancer (breast, colorectal, and prostate cancer) have improved survival rates when diagnosed in summer rather than winter in the U.S. [75], though mortality rates are not consistently increased in winter.

4. Discussion

The broad summer–winter seasonality of death rates seems to be due, primarily, to seasonal variations in solar UVB doses affecting serum 25(OH)D concentrations. Seasonal variations in temperature seem to play a minor role. However, several features do not fit this pattern. The first is the excess death rates at Christmas and New Year's Day. The explanation by Phillips and colleagues [1] that the rates may be due to overworked staff at hospital emergency departments seems plausible, but that requires investigation. A second anomaly occurs over days 25–80

(approximately January 25–March 21). This period corresponds to the time of lowest 25(OH)D concentrations in the U.S. and is later than the period of coldest ambient temperature. No major holidays fall during this second anomalous phase; thus, the excess death rates may be due to low 25(OH)D concentrations, together with the increases in clotting tendency, and platelet stickiness, that follow exposure to severe cold. A third anomaly occurs near day 270 (September 26 in non–leap years). This time corresponds to a few weeks after school resumes and is a time when school children are exposed to bacteria and viruses they have not encountered recently. Children bring the microbes home and pass them on to their family members. For example, a study in Israel examined the rate of influenza-like diagnoses in schoolchildren and their family members during the winter months of 1998–2002, when a nationwide elementary school strike occurred. During the strike year, the rate of influenza infection dropped sharply 2 weeks after the start of the strike in 2000 [76]. A later study in eight European countries found reductions of about 20% for common infectious diseases when school was closed for weekends or regularly scheduled holidays [77]. The study that reported minimum mortality rates in September in Mediterranean countries compared with August in northern European countries gave as a possible reason longer summer vacations in the south and greater vitamin D production [4]. Summer school vacations are 3 months in southern European countries, compared with 2 months for northern European countries [78].

Infectious diseases are a risk factor for deaths from CVD. Influenza has often been found as a trigger for acute myocardial infarction or other deaths from CVD [79]. Among U.S. veterans of mean age 73 years who had laboratory-confirmed influenza between October 2010 and December 2012, 25% had evidence of acute cardiac injury shortly thereafter [80].

A fourth anomaly begins near day 327 (November 23), about when Thanksgiving is celebrated. Thus, it could also be related to increased population mixing due to travel for the holiday with a resulting increase in the incidence of infectious diseases.

5. Policy implications

Several factors seem to underlie phases of increases in the death rate in the U.S.: low solar UV doses, low 25(OH)D concentrations, spread of infectious diseases through population mixing, overworked hospital emergency departments, and low temperatures. Influenza vaccinations can reduce the risk of influenza to some extent, but the effectiveness seems to be higher for children than for the elderly. One study of a vaccine with three strains in the 2010–2011 influenza season found 69% effectiveness for children aged 6 months–8 years but only 38% for adults older than 65 years [81]. Ambient temperature effects can be minimized by domestic heating and by wearing warm clothing. However, for many people living where it is cold in winter, heating bills in winter may limit the amount of heating used. Population mixing is a normal part of living and is not likely to change.

We cannot yet exclude the effects of other confounding factors, such as other aspects of nutrition, possible variations in mortality with season of birth, variation in birth size, or genetic, or as yet unrecognized factors. However, a previous study estimated that doubling 25(OH)D concentrations at the population level could reduce mortality rates by 10%–20%, adding about 2 years to overall adult life expectancy [82].

One meta-analysis used results from 32 prospective studies (including several with participants who had chronic or infectious disease) to look at all-cause mortality rate. For 25(OH)D concentrations <36 ng/mL, the study found a nearly linear increase in mortality rates toward lower 25(OH)D concentrations but saw no change above 36 ng/mL [43]. For most people, maintaining a serum 25(OH)D level of at least 36 ng/mL (90 nmol/L) would take an oral intake of 1500–4000 IU/d of vitamin D_3 [83]—intakes within the current Institute of Medicine safe recommendations [84].

These several factors leave increasing 25(OH)D concentrations as a relatively easy and effective means to reduce the risks of the diseases discussed and to increase life expectancy. While vitamin D_3 supplementation would be more important in winter than in summer, supplementation and increased UVB exposure would still be required in summer to have everyone achieve 25(OH)D concentrations >36 ng/mL since the population mean value in summer in the U.S. is 28 ng/mL [15].

6. Conclusions

Much of the seasonal variation in all-cause mortality rates appears to be due to seasonal variations in solar UVB doses and resulting changes in 25(OH)D concentrations. Several other factors also explain some of the observed seasonal variations in mortality rates. Public health policies that advised people to maintain their 25(OH)D concentrations above 36 ng/mL year-round through sensible sun exposure, vitamin D_3–fortified food, and vitamin D_3 supplements should help reduce death rates and increase life expectancy. The recent decision by the U.S. Food and Drug Administration to permit fortifying milk and milk products with the equivalent of 800 IU of vitamin D per quart [85] is a step in the right direction, and other countries should consider increasing their vitamin D intake recommendations similarly.

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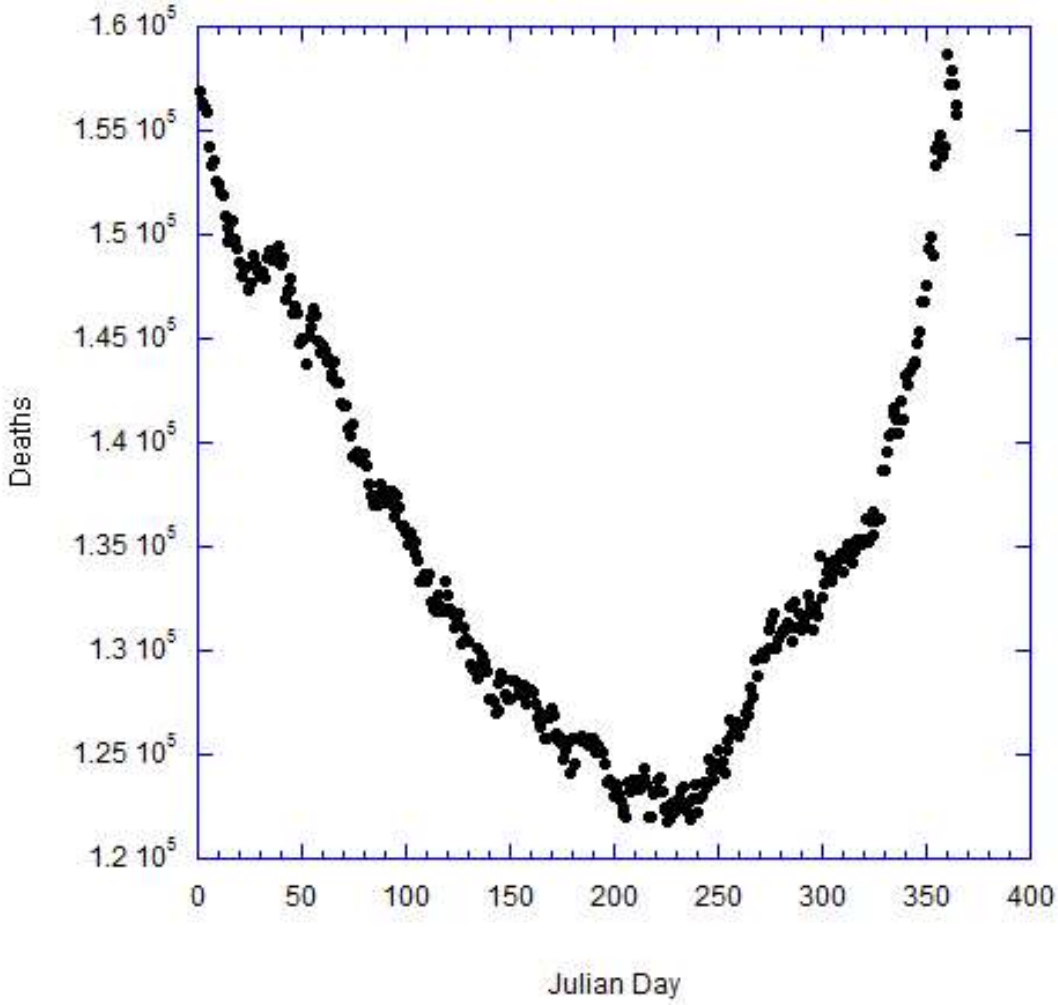

Figure 1. Deaths per day of the year, according to all official U.S. death certificates for 1979–2004 from Phillips et al., 2010.