Clinic Rev Bone Miner Metab (2009) 7:63–76
DOI 10.1007/s12018-009-9039-5

ORIGINAL PAPER

Health Disparities and Vitamin D

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Published online: 18 April 2009

Abstract Research over the last two to three decades has slowly demonstrated that Vitamin D, a long neglected and unappreciated hormone, is of profound importance to human health and survival. Vitamin D begins its synthesis in human skin with ultraviolet B radiation (UVB) from the sun. Melanin is a potent UVB blocker, protecting the skin from the high intensity sunlight found on the tropical savannah into which humans evolved, but not impairing the skin's ability to synthesize generous quantities of vitamin D there. Adaptation to environmental availability of UVB radiation from the sun appears to explain the variation in skin melanin content in indigenous human populations around the world. Evidence shows populations in the United States have mean vitamin D levels that are associated with the relative amount of melanin in the skin in those populations, and that humans with insufficient levels of vitamin D suffer disproportionately from the diseases associated with health disparities. The differences in incidence and severity of cardiovascular diseases, the most common cancers, diabetes, tuberculosis, conditions associated with infant mortality, and total mortality in populations associated with health disparities in the United States are explored in this chapter. Indeed, the magnitude of the disparity in diseases associated with "health disparities," related to the effect of vitamin D on those diseases, is such that eliminating the differences in vitamin D levels between the populations would appear to virtually eliminate the health disparities between them.

Keywords Health disparities · Vitamin D · Ultraviolet B (UVB) radiation · Melanin · Infant mortality

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Introduction

The impetus to identify and address health disparities in the United States began with the recognition of a persistent relatively fixed disparity in the life expectancy for populations classified as white and black in the United States (Fig. 1).

The US National Institutes of Health (NIH) convened a working group in 1999 in response to a Clinton Administration directive to develop a strategic plan for reducing "health disparities." That group issued the following definition: "Health disparities are differences in the incidence, prevalence, mortality and burden of diseases and other adverse health conditions that exist among specific population groups in the United States" [1]. The Center for Disease Control (CDC) Office of Minority Health and Health Disparities (OHMD) takes the position that "Compelling evidence that race and ethnicity correlate with persistent, and often increasing, health disparities among US populations demands national attention." And that "Current information about the biologic and genetic characteristics of minority populations does not explain the health disparities experienced by these groups compared with the white, non-Hispanic population in the United States" [1]. As part of its Healthy People 2010 Initiative, the US Department of Health and Human Services (HHS) selected six focus areas in which racial and ethnic minorities experience serious disparities in health access and outcomes. HHS also identified additional diseases and conditions which disproportionately impact racial and ethnic minorities (Table 1) [2].

This chapter will address the likelihood that vitamin D deficiency is a major factor in health disparities between populations in the United States, and particularly between the Non-Hispanic White (NHW) and Non-Hispanic Black

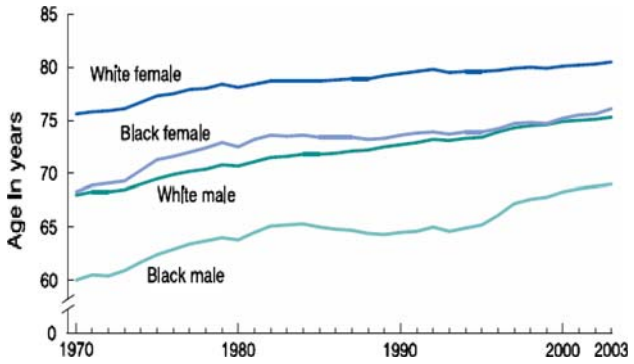

Fig. 1 Life expectancy at birth by race and sex: 1970–2003 (From the CDC National Vital Statistics Reports, Vol 54, No 14, United States Life Tables, 2003)

Table 1 From the US Department of Health and Human Services, Office of Disease Prevention and Health Promotion, Healthy People 2010 Website, http://www.healthypeople.gov

Healthy people 2010 focus areas	Other diseases of health disparity
Cancer screening and management	Mental Health
Cardiovascular disease (CVD)	Hepatitis
Diabetes	Syphilis
HIV infection/AIDS	Tuberculosis (TB)
Immunizations	
Infant mortality	

(NHB) populations between whom there is most often the widest health disparities and about whom there is the greatest documentation. The Hispanic population usually falls in the midrange between those populations on measures of health disparities as its mean serum vitamin D levels fall midrange between the levels of those non-Hispanic populations.

Mattapan Community Health Center (MCHC), where the author of this chapter serves as Medical Director, became interested in the role of vitamin D deficiency as major factor affecting the health disparities noted in our community, which census figures identified as 92% black, compared with the city of Boston as a whole (in which our community is located). MCHC has been publishing an annual community health report card for several years as part of its yearly health outreach event "Health Care Revival" [3]. A chance reading of Moskilde's review article [4] lead to a review of research into vitamin D, and subsequently prompted an investigation into the possibility that vitamin D deficiency might affect the incidence of low birthweight babies and infant mortality, a significant problem in Mattapan that MCHC had been founded in 1972 to address. The search for references on this relationship took place in May 2006, just a month after Mannion et al. (vide infra) had published their study on the correlation of vitamin D and milk intake with birthweight. Testing of 25(OH)D levels of random patients whose insurance would cover the cost, along with a cohort of prenatal registration patients, revealed a high prevalence of vitamin D deficiency in our population in the early months of 2007.

Vitamin D sufficiency is now accepted to be represented by serum levels of 25-hydroxyvitamin D (25[OH]D) of at least 30 ng/ml, with serum levels from 20–30 ng/ml considered to be insufficient and levels below 20 ng/ml deficient, by reference to levels consistent with maximal absorption of calcium from the gut and plateauing (at baseline) of parathyroid hormone (PTH) levels. However, optimal levels of vitamin D for health have been demonstrated to be even higher by measure of maximal rate of bone mineral deposition (36–40 ng/ml) [5]. Lower extremity muscle function, rate of fall prevention in the elderly, rate of fracture prevention, and depression of colorectal cancer incidence all appear to be maximal at 25(OH)D levels greater than 48 ng/ml, though by that level the rates of change in the measures are approaching minimal [6].

The Third National Health and Nutrition Examination Survey (NHANESIII) found NHWs have a mean serum level of 25(OH)D of 32 ng/ml (Fig. 2). It found NHBs have a mean 25(OH)D of 19 ng/ml while those labeled Hispanic had a mean 25(OH)D of 25 ng/ml [7]. By these measures a substantial proportion of the population in the United States has suboptimal vitamin D levels. It is also quite evident that there is a large disparity in the levels of vitamin D sufficiency in the populations noted, and that to the extent that vitamin D is important to human health, this will be manifested in disparate health between the populations.

Infant Mortality

Infant mortality rates in the United States vary by racially and ethnically categorized subpopulations. The 2003 US infant mortality rates from the CDC National Vital

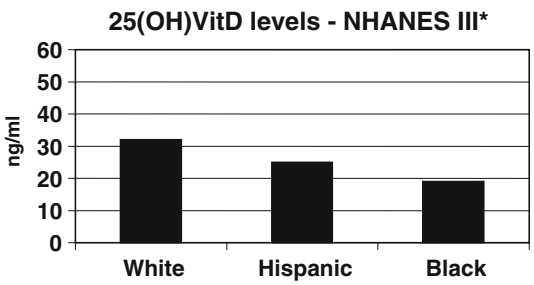

Fig. 2 25(OH)VitD levels—NHANES III* (Bibuld D, Data from [7])

Statistics Reports (NVSR) Health of the US are shown in Fig. 3. Similarly to the overall mortality rates for the US populations, there has been a persistent infant mortality disparity between the black and white populations (Fig. 4).

Short gestation and low birth weight (SGLBW) were among the most important predictors of infant survival in the overall US population, second only to congenital malformations, deformations and chromosomal disorders (CMDCD) in 2004 [8]. Sudden Infant Death Syndrome (SIDS) ranks third as a cause of death.

In 2004 an analysis of the five leading causes of infant mortality showed significant differences in the proportions of death attributable to those causes in different ethnic populations. Specifically, while the number one cause of death was CMDCD in the Non-Hispanic White (NHW) and Hispanic populations, the rate of CMDCD in the Non-Hispanic Black (NHB) population was only 56% that of disorders of short gestation and low birth weight (SGLBW) [8]. Accordingly, while death rates in the NHB population from CMDCD were 29% higher than the NHW population, the death rate from SGLBW was 285% higher, or almost four times as much. Thus SGLBW was the leading cause of infant mortality for the NHB population [8].

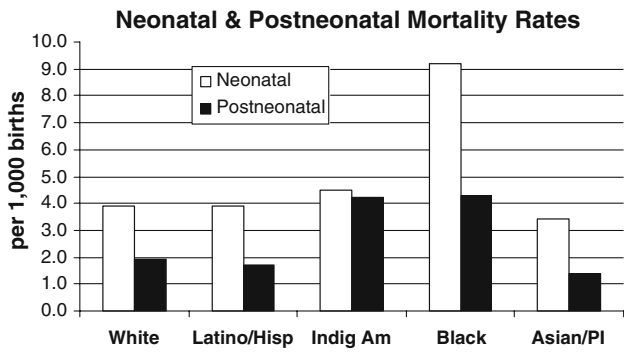

Fig. 3 Neonatal and postneonatal mortality rates (Bibuld D, Data assembled from Health, United States 2006—Table 19 Linked Birth/Infant Death Data Set, National Center for Health Statistics, CDC)

Gains in neonatal survival in the United States have been largely due to increases in survival of SGLBW babies. Currently, among very low birth weight babies and very premature births, the mortality rate does not reach 50% of babies born except for those born below 500 g, or at less than 24 weeks of gestation. For babies born at less than 3500 g and less than 37 weeks gestation, neonatal mortality is lowest among NHB of the three ethnic groups [9]. It is highest in that group for NHWs.

Despite that, in 1995 through 1997 the overall mean birth weight for babies born to NHB resident mothers in the US was 3133 g; that for NHW babies was 3413 g. The percentage of infant mortality in the NHB population attributable to birth weight less than 750 g (or VLBW) was 63.6%. This compared to 42.9% of infant mortality for Hispanic and 38.9% for White babies (Fig. 5). The incidence of VLBW babies born was 85 in NHB, 25 for Hispanic and 20 for NHW per 10,000 births. Similarly, for infants born at less than 28 weeks gestation, the incidence among the NHB, Hispanic, and NHW populations were 139, 45, and 35 per 10,000 births, respectively (Fig. 6). The percent of mortality attributable to these very short gestation births was 44.6, 48.7, and 68.6% for NHW, Hispanic, and NHB populations, respectively [9].

Similarly, though less dramatically, there was disparity in incidence of overall prematurity and LBW. Babies born at less than 2500 g were 1155, 538, and 491 per 10,000, and born at less than 37 weeks gestation were 1587, 987,

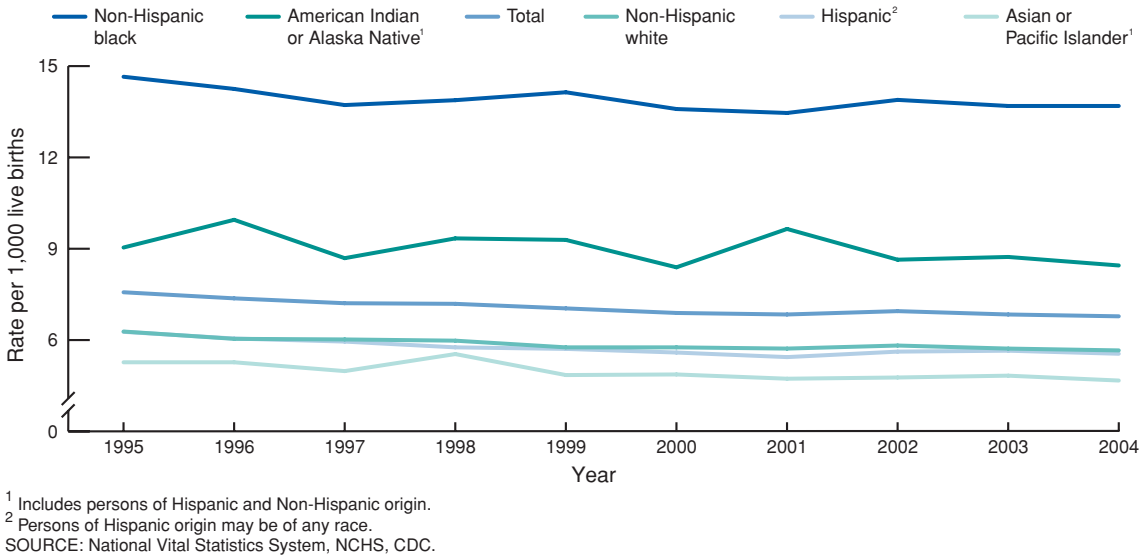

Fig. 4 Overall mortality rates for the US populations [8]

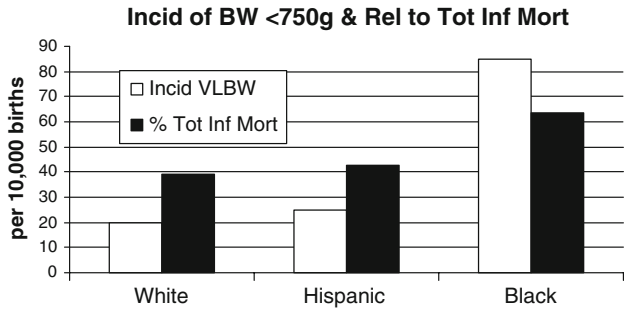

Fig. 5 Incid of BW <750 g and Rel to Tot Inf Mort (Bibuld D, adapted from Adapted from [9])

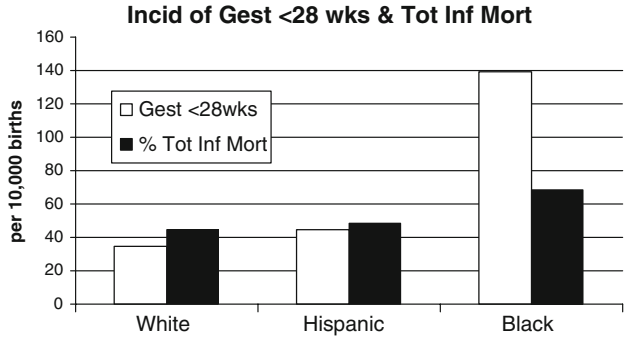

Fig. 6 Incid of Gest <28 weeks and Tot Inf Mort (Bibuld D, adapted from adapted from [9])

and 803 per 10,000 births (Fig. 7) in the NBH, Hispanic, and NHW populations, respectively [9] These figures show the incidence of SGLBW babies to be inversely proportional to serum levels of 25(OH)D in mothers and infants in these populations (as will be shown). The incidence of infants born at greater than 4000 g shows the opposite skew to that seen in SGLBW (as would be expected), being 536, 905, and 1233 per 10,000 births in the NHB, Hispanic, and NHW populations. The incidence of larger babies directly correlates with the levels of 25(OH)D in the respective populations (Fig. 2).

The death rate from SIDS in the NHB population was 105% higher than the NHW population [8]. SGLBW is a major risk factor for SIDS. Age of mother and maternal smoking history are the two major maternal risk factors for SIDS [10]. The incidence of cigarette smoking in the US for NHB mothers was only 61% (at 8.4%) that of NHW mothers (13.8%) in 2004. The rate for Hispanic mothers was 2.6%; for AI/AN mothers the rate was 18.2% [11]. The rate of birth to mothers aged 15–19 years was 6.3% for NHB, or 67% higher than for NHW mothers (3.8%) at the same age. This data suggests that the SGLBW rate in NHB neonates is the major factor in the higher rate of SIDS in this population.

The vitamin D status of the neonate and fetus appear to be totally dependent on Vitamin D stores of the mother and specifically maternal 25(OH)D [12–15]. Various studies show fetal cord blood at birth containing 50–70% of maternal 25(OH)D levels [12–16]. They also show that when vitamin D supplementation is given to mothers, serum 25(OH)D in maternal and fetal cord increases in roughly the same proportion [12, 14, 16]. There is no significant correlation between fetal and maternal serum levels of 1,25(OH)D [14].

Vitamin D deficiency has been well documented to be much more common in the NHB population in the United States than the NHW population. The Hispanic (or Latino) population as a whole have serum levels of 25(OH)D roughly midway between the black and white populations, being 25 ng/ml (Fig. 2) [7, 15, 17–21]. This disparity in serum 25(OH)D is apparent throughout the age spectrum, and has been particularly well documented in women of child bearing age, and in pregnant women (Fig. 8) [15, 17, 18, 20–22]. The 25(OH)D levels have been shown to be disparate in neonates as well [15, 23].

In data taken from the third National Health and Nutrition Examination Survey (NHANES III) [21] from 1988 to 1994, 1546 NHB and 1426 NHW non-pregnant women aged 15–49 were evaluated after exclusions for a number of variables. The NHB women had a mean serum 25(OH)D concentration of 17.7 ng/ml. The NHW women's serum 25(OH)D levels averaged 33 ng/ml. Similarly, Bodnar et al. [22] studying 200 NHB and 200 NHW pregnant women in Pittsburgh, found initial serum values (at 4–21 weeks of gestation) of 25(OH)D of 16.1 ng/ml

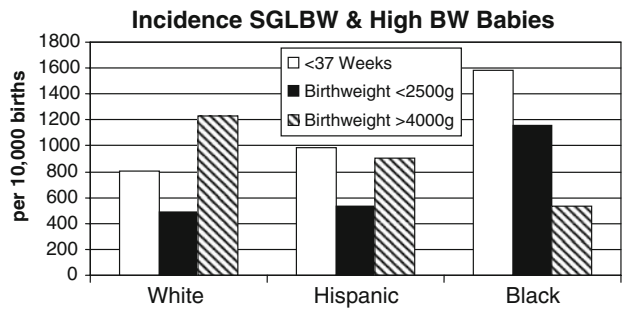

Fig. 7 Incidence SGLBW and high BW babies (Bibuld D, adapted from adapted from [9])

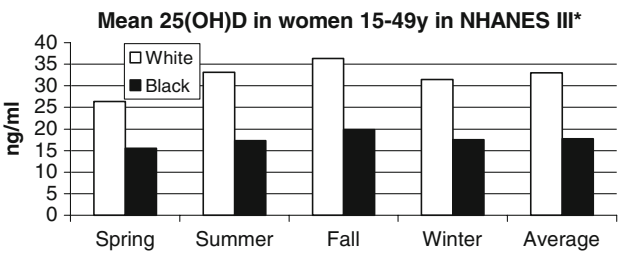

Fig. 8 Mean 25(OH)D in women 15–49 years in NHANES III* (*Adapted by Bibuld D, from [21])

and 29.2 ng/ml in the respective cohorts. Women who did not carry to term were excluded from these values. A total of 90% of the women were taking prenatal supplements during the last 3 months of pregnancy. At birth (37–41 weeks) the NHB mothers showed a mean serum level of 19.8 ng/ml, and their cord blood 15.6 ng/ml. For NHW women the values were 32.2 ng/ml for serum and 26.9 ng/ml in cord blood at term [22].

Vitamin D deficiency has been correlated with SGLBW babies [12, 24–27]. In 1980 in response to recognition of a high incidence of pregnancy associated osteomalacia, and decreased fetal size in association with vitamin D deficiency among Asian (primarily Indian) women in England, Brooke et al. [26] evaluated vitamin D supplementation in Asian women. That study included 59 pregnant women given 1000 IU/day in their last trimester, and a matched group of 67 women given placebo. They reported modest increase in birth weight of 123 g in the treatment group. The baseline maternal levels of 25(OH)D before supplementation (at 28 weeks) was 8.0 ng/ml. The term blood levels reported of 25(OH)D in the treated mothers (67.2 ng/ml) is highly inconsistent with expected increase in serum 25(OH)D levels at the reported level of supplementation (~18 ng/ml). However, incidence of SGA infants was 28.6% in the control group versus 15.3% in the treated group. SGA was defined as weight less than the tenth percentile. Weight gain in the treated mothers increased significantly more (63 g/day) than in the control group (46 g/day). European women typically gain 71 g/day in their last trimester [26]. Significantly, the increase in birth weight of 123 g found in the treated group, who received up to 84,000 IU of vitamin D during the third trimester of pregnancy (or the equivalent of 300 IU per day for the entire pregnancy) is in accordance with the weight gain associated with the differential in vitamin D intake found by Mannion et al. [24] as noted below. In a follow-up study Brooke et al. [28] showed that the weight difference between the infants in the treated group increased modestly from birth through the first year, and was 490 g greater at the end of 1 year. The length of infants from the treatment group was 3.3 cm (or 0.33 dm) greater at 1 year as well (Fig. 9).

Marya et al. [27] studied 25 women treated with 1,200 IU of vitamin D a day in their third trimester, 20 women treated with 2 doses of 600,000 IU in the 7th and 8th months of pregnancy and 75 women who received no supplemental vitamin D in a study published in 1980. They reported a significantly greater increase in birth weight with either vitamin D supplementation, but greater increase with the 600,000 IU doses.

Brunvand et al. [29] evaluated 30 Pakistani women in Norway to look at the relation of elevated serum parathyroid hormone (PTH) levels, serum ionized calcium levels and their relation to reduced fetal growth in vitamin D deficient pregnant women. Women with complicated pregnancies were excluded. A total of 29 out of the 30 women had 25(OH)D levels below 12 ng/ml. Thirteen of them had high PTH levels. A positive correlation was found between the maternal serum ionized calcium level, and a negative correlation noted for serum PTH level, with crown-heel length of the fetus. PTH elevation and hypocalcemia are both complications of low vitamin D levels.

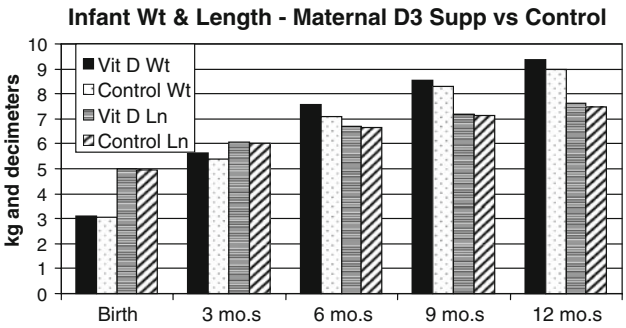

Fig. 9 Infant weight and length—maternal D_3 supp versus control (Bibuld D, adapted from Adapted from [28])

Specker [30], in her review of studies of maternal and neonatal outcomes in vitamin D deficiency, reports on a study by Marya et al. [31], published in 1988. A total of 100 women were given 600,000 IU 25(OH)D in both the 7th and 8th month of gestation and compared to 100 pregnant women who were not supplemented. Serum 25(OH)D levels were not reported, but greater birth weight and size were reported for infants born to the treated cohort.

Mannion et al. [24] evaluated the relationship of vitamin D intake through fortified milk in 279 pregnant women in Calgary, Alberta. Seventy-two of them reported intake of one cup of milk or less daily (restricted intake). A total of 207 drank more milk than one cup daily (unrestricted). It was calculated that the restricted group took in on average 316 IU vitamin D daily, compared to 524 IU per day in the unrestricted group. The birth weight of infants born to mothers in the restricted group was 3410 g and was 3530 g in the unrestricted cohort (Fig. 10). It was calculated that for each increase in daily intake of vitamin D by 40 IU, there was a corresponding increase in birth weight of 11 g. By extrapolation, this suggests a possible weight gain of 550 g with 2,000 IU vitamin D supplementation daily from the beginning of pregnancy (Fig. 11).

Vitamin D deficiency has also been associated with an increased incidence of pre-eclampsia, elevated BPs in pregnant women, hypocalcemia, and hypocalcemic seizures in neonates, craniotabes, and other disorders of fetal development. However, documentation on the relationship of these disorders to overall infant mortality is lacking, and therefore they are not addressed here.

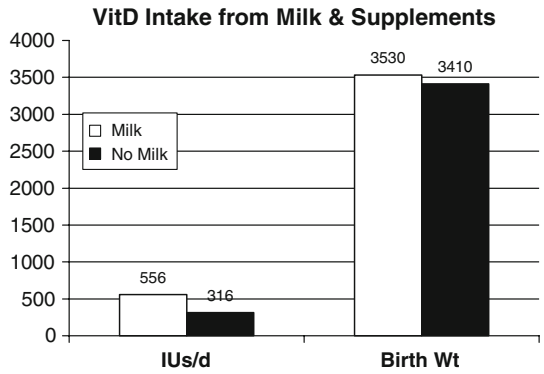

Fig. 10 VitD intake from milk and supplements (Bibuld D, from [24])

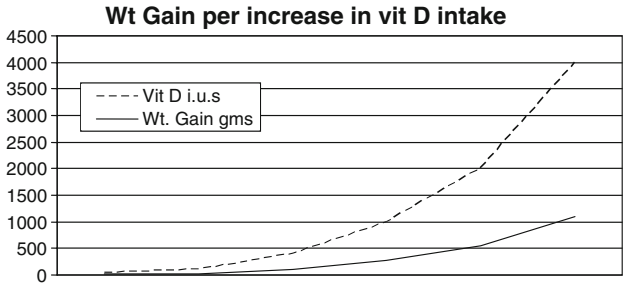

Fig. 11 Weight gain per increase in vit D intake (Bibuld D, from [24])

Infant mortality remains one of the most dramatic markers of health disparity in the United States. SGLBW babies are the most important component to that disparity, including their impact on the disparity in infant deaths due to SIDS. Abundant data tie the incidence of SGLBW to low maternal serum levels of 25(OH)D. Infant mortality and birth data demonstrate the inverse relationship of 25(OH)D levels with the incidence and severity of SGLBW in ethnically and racially defined populations. Evidence also shows that vitamin D supplementation increases birth weight and appears to reduce the incidence of SGLBW births.

Unfortunately, the number of studies and subjects in those studies of supplementation are limited, and many questions remain unresolved. There is not enough data to suggest whether there is a threshold of circulating vitamin D for optimal outcomes, or whether improvement in weight gain and outcome is linearly related to vitamin D level. It does not appear that enough vitamin D has been given to mothers to raise their levels as high as optimal levels have been shown to be for dental attachment, maximal muscle strength, colon cancer prevention, and fracture prevention (levels above 48 ng/ml) [5]. Work that Hollis, Wagner et al. are doing in South Carolina compares supplementation of vitamin D with from 400 to 6000 IU a day beginning in early pregnancy should be helpful in answering some of these questions.

Cardiovascular Disease

Cardiovascular disease, including hypertension and cerebrovascular disease, is more prevalent and causes higher mortality in the black population in the United States than in the white population (Fig. 12) [32, 33].

Risk factors traditionally associated with cardiovascular disease include family history, hyperlipidemia, smoking, diabetes mellitus, obesity, sedentary lifestyle, and the presence of hypertension itself. Recent research also strongly identifies hypovitaminosis D as a major risk factor for heart disease, and perhaps the most important risk factor in the United States [34, 35].

Evidence suggests several mechanisms by which vitamin D may protect against cardiovascular disease. These include inhibition of inflammatory cytokines and stimulation of production of anti-inflammatory cytokines (thereby inhibiting initiation of atherosclerosis), inhibition of smooth muscle proliferation (inhibiting vascular media thickening), inhibition of myocardial cell hypertrophy, inhibition of the renin-angiotensin system, and prevention of arterial calcification [36–38].

Martins et al. [7] reported on the relationship between cardiovascular risk factors and serum levels of vitamin D. Their review of data from over 15,000 persons who participated in NHANES III made comparisons between those in the lowest quartile of serum 25(OH)D (less than 21 ng/ml) with those in the highest quartile (more than 37 ng/ml). It found that those in the lowest quartile had a 35% higher likelihood of hypertension, over twice as likely to have pre diabetes or diabetes, over twice as likely to be obese, 38% more likely to have elevated triglycerides, and 26% more likely to have elevated cholesterol.

In May 2007, Forman et al. [39] looked at the likelihood of developing hypertension in 613 males participating in the Health Professionals' Follow-Up Study (HPFS) and in 1198 women from the Nurses' Health Study. None of these professionals had hypertension when they entered the study. The two groups were compared by levels of serum 25(OH)D. Among the men, the chance of developing hypertension with a 25(OH)D level of less than 15 ng/ml

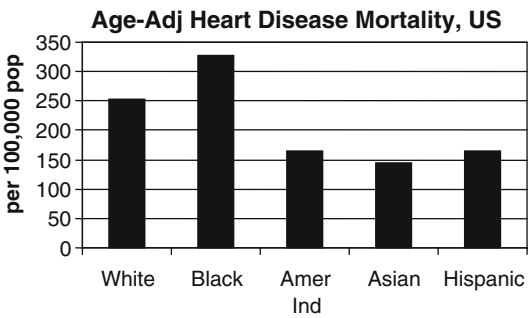

Fig. 12 Age-adj heart disease mortality, US (Bibuld D, from [32])

was more than six times higher than men with a 25(OH)D level of more than 30 ng/ml after 4 years. Among the women, the chance of developing hypertension was almost three times higher for the low vitamin D group compared to the higher level (Fig. 13).

Wang et al. [34] reported on the impact of vitamin D levels in cardiovascular disease in 1739 Framingham, MA patients with no evidence of cardiovascular disease (angina, heart attack, stroke, TIA, peripheral artery disease, or heart failure) at the start of the study. They were followed for the development of cardiovascular disease during the course of the study. The participants had an average age of 59 years, were 55% women, and all white (owing to the history of the participants followed in study which originated in the 1940s). The study compared patients with serum 25(OH)D levels <15 ng/ml D with those with levels ≥15 ng. It found that those with the lower levels of 25(OH)D had more than twice the incidence of cardiovascular disease than those with the higher levels after 5 years of follow-up. For patients with hypertension the risk of cardiovascular disease was two and a half times higher in the group with lower 25(OH)D. And while the risk of cardiovascular disease was 65% higher in those patients with hypertension and higher 25(OH)D, than those without hypertension and higher 25(OH)D, it was over 300% higher (or four times as great) in those with lower vitamin D levels and hypertension than those with higher 25(OH)D and no hypertension. It was also reported that those with 25(OH)D <10 ng/ml had even greater risk than those who had a 25(OH)D of 10–15 ng/ml. Additionally, analysis showed that the probability of developing cardiovascular disease with normal blood pressure and lower 25(OH)D (less than 15 ng/ml) was greater than the chance of developing cardiovascular disease with high blood pressure and the higher level of vitamin D (at least 15 ng/ml) after 7 years of follow-up.

In June 2008, Giovanucci et al. [35] reported on a prospective, nested case-controlled, study involving men free of cardiovascular disease in the 18,255 man HPFS who were followed for development of fatal and non-fatal MI and had blood samples collected for 25(OH)D. A total of 454 men who had events were matched 2:1 with controls matched by age, date of blood collection, and smoking status. Compared with subjects whose 25(OH)D levels were ≥30 ng/ml, those whose levels were lower than 15 ng/ml had a relative risk (RR) for MI of 2.42 (Fig. 14). Subjects whose 25(OH)D level were between 24 and 30 ng/ml had intermediate risk.

Dobrig et al. [40] reported on 3258 consecutive male and female patients undergoing coronary arteriography in Austria. They found twice the mortality for cardiovascular disease (RR of 2.22) for patients in the two lower quartiles of 25(OH)D (means of 7.6 and 13.3 ng/ml), than among patients in the highest quartile (median 28.4 ng/ml). The graphic data presented show a linear relationship between the quartile of 25(OH)D level and cardiovascular mortality risk (Fig. 15).

In August 2008, Melamed et al. [41] in an analysis of NHANES III data found an unadjusted increase of cardiovascular mortality of 70% (RR 1.70) among 13,331 participants aged 20 years or more in participants in the lowest quartile of 25(OH)D levels (<17.8 ng/ml) compared with those in the highest quartile (>32.1 ng/ml). Non-Hispanic blacks, Mexican Americans, and the elderly were oversampled in this study to allow for more precise estimates for those groups. When adjusted for age, race, sex, season, hypertension, CVD history, diabetes, smoking, HDL, total cholesterol, use of anti-lipids medication, GFR, albumin, albumin/creatinine ratio, C-reactive protein level,

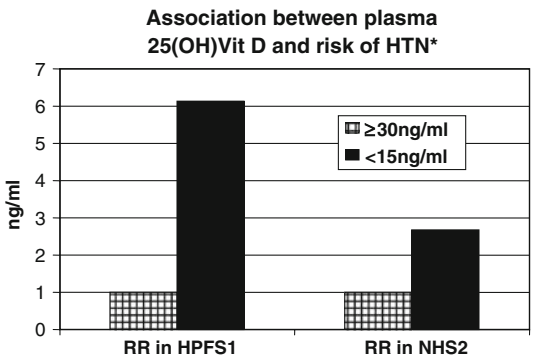

Fig. 13 Association between plasma 25(OH)Vit D and risk of HTN* (Bibuld D, from [39])

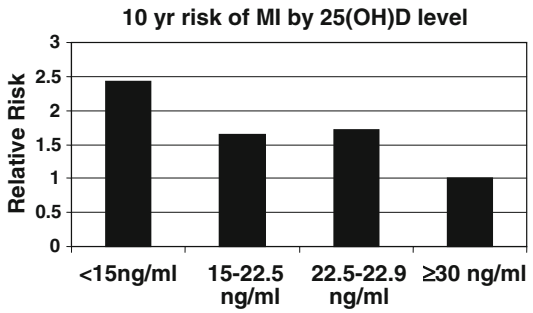

Fig. 14 A 10 year of MI by 25(OH)D level (Bibuld D, from [35])

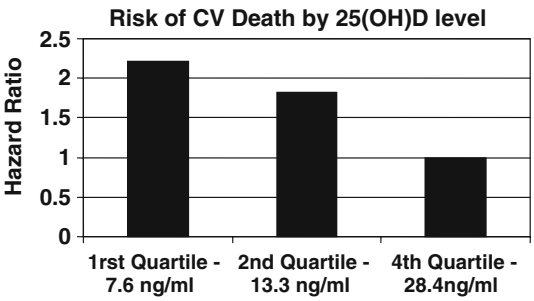

Fig. 15 Risk of CV death by 25(OH)D level (Bibuld D, from [40])

BMI, physical activity, use of vitamin D supplementation, and low socioeconomic factor they still found a 20% increase in cardiovascular mortality between the quartiles. In their study they also reported on the vitamin D profiles of population groups in study and found that for non-Hispanic whites 43.5% were in the highest quartile of 25(OH)D level of the general population, and only 9.5% fell into the lowest quartile), while only 7.8% of non-Hispanic blacks fell into the highest quartile, and 50.3% were in the lowest quartile.

Cancer

Cancer is a heterogeneous group of diseases with multifactorial etiologies, many of which remain to be elucidated. The mechanisms of vitamin D's inhibition of development, growth, and spread of cancer are addressed elsewhere in this volume. An article by Garland et al. [42] published in February 2006 referred to over 1000 laboratory and human population studies published concerning the association of vitamin D and cancer up until then.

There are major differences in the incidence of overall and individual cancers in different ethnically categorized subgroups in the US, with NHB and NHW having higher incidence and mortality than other subgroups (Fig. 16) [43]. NHBs not only have a higher incidence of cancer compared to NHWs, but as significantly, the mortality rates of NHBs with cancer are higher than NHWs. Despite having a significantly lower incidence of cancer than those two population subgroups, AI/ANs have the highest ratio of mortality to incidence for cancer, while the rates of Hispanics and Asian/PIs are the lowest for all three measures. Some of the difference in mortality rates may be reflective of past differences in cigarette smoking (by comparison of mortality/incidence ratios to prevalence of cigarette smoking) [44]. Currently, tobacco use is less in NHBs than NHWs, and least in Hispanics [45].

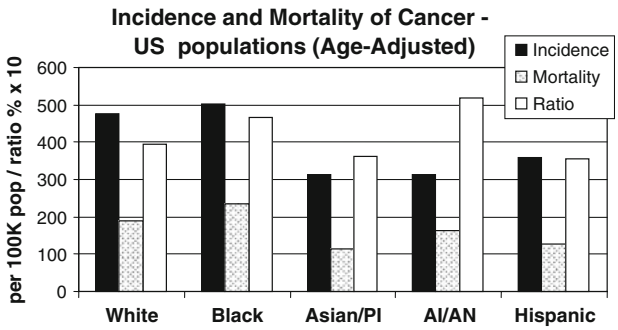

Fig. 16 Incidence and mortality of cancer—US populations (age-adjusted) (Bibuld D, from [43])

Lung, breast, and colorectal cancers were responsible for 51% of cancer mortality during 1975–2005 in both NHW and NHB women [43]. Lung, prostate, and colorectal cancers were responsible for 51% of NHW male cancer death in that same period, but 59% in NHB males largely due to the greater impact of prostate cancer on mortality in that population. In all populations lung cancer was the greatest killer.

During the period of 1992–1999 NHBs had an age-adjusted incidence of cancer that was ten percent higher than NHWs. In females, the incidence of cancer was actually 5% higher in NHWs than in NHBs. In males NHBs had an incidence 24% higher. Mortality was 30% higher for NHBs than NHWs during the same period, being 19% higher for NHB females, and 43% higher for NHB males than their NHW counterparts (Fig. 17) [46].

The period of 2001–2005 showed modest decreases in the incidence and more significant decreases in mortality in cancer for US populations, but significant disparities remained, especially in mortality [43]. The incidence of cancer in NHBs was 5% higher for the period compared to NHWs, but mortality was still 24% higher. In females, the incidence of cancer was 6% higher in NHWs than in NHBs. In males NHBs had an incidence 18% higher than NHWs. Mortality was 17% higher for NHB females and 36% higher for NHB males than NHW females and males, respectively.

Giovannucci et al. [47] developed a multiple linear regression model using multiple determinants of vitamin D exposure, including skin pigmentation, diet, and vitamin D supplementation to compute the relative risk of cancer incidence and mortality based on serum 25(OH)D level in men from the HPFS. Their model found that an increase of 10 ng/ml of 25(OH)D was associated with a 17% reduction in cancer incidence and a 29% reduction in cancer mortality.

Looking at cancer incidence and mortality among black and white male health professionals from the same data (involving a total of 481 black and 43,468 white men over 16 years) Giovannucci et al. [48] concluded that blacks with low risk factors for hypovitaminosis D (average serum

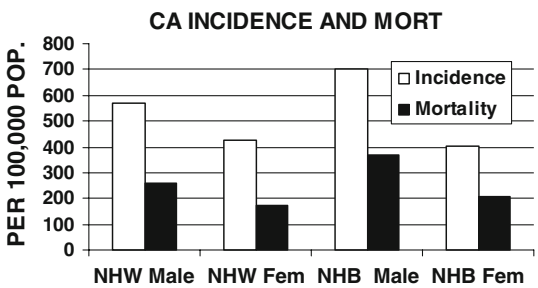

Fig. 17 CA incidence and MORT (Bibuld D, from [46])

25(OH)D 21.6 ng/ml) had similar incidence and mortality (RR 0.95 and 1.55, respectively) to whites with low risk factors (average 25.8 ng/ml) for cancer. Blacks with additional risk factors for poor vitamin D status (average 17.2 ng/ml) had much higher risks for cancer incidence and mortality (RR 1.57 and 2.27) compared to whites with low risk factors. Whites at higher risk for hypovitaminosis D averaged 23.1 ng/ml and had higher incidence and mortality than whites with lower risk, but lower mortality than blacks with higher risk.

Lappe et al. [49], in a 4 year study of vitamin D and calcium supplementation in 1179 women (all white) in eastern Nebraska, showed a 77% reduction in the incidence of cancer during the second to fourth years of the study with supplementation compared with placebo. The decrease in incidence was associated with an increase of serum 25(OH)D from a baseline of 28.7 to 38.4 ng/ml after 12 months. After 12 months the calcium supplement and placebo arms remained close to baseline at 28.4 ng/ml each. While there was a lesser reduction in cancer incidence with calcium supplementation alone, it did not reach a level of significance (Table 2).

Lung cancer incidence is 36% higher and mortality 31% higher in NHB males than NHW males. The incidence and mortality are slightly lower for NHB females than for NHW females (Fig. 18).

Lung cancer incidence appeared to be reduced by 15–20% in males associated with an increase of 10 ng/ml in serum 25(OH)D according to Giovannucci et al. [47]. Lappe et al. [49] found only one case of lung cancer in the Vitamin D supplemented group (403 subjects) compared with 3 in the placebo group (266 subjects). Zhou et al. [50] found that patients with stage 1B-2B non small cell lung cancer had a 55% better survival rate up to 12 years after diagnosis if serum levels of 25(OH)D were >21.5 ng/ml (highest quartile in their study) compared with <10.2 ng/ml (lowest quartile) (Table 3).

Colorectal cancer incidence was 22% higher in NHBs than NHWs in 2001–2005 [43]. The mortality was 42% higher in NHBs (Fig. 19). Numerous studies have shown significant decrease in incidence of colorectal cancer in the range of 50% with vitamin D supplementation and with adequate levels of serum 25(OH)D [51–54].

The incidence of breast cancer in NHBs was only 90% that of NHWs in 2001–2005. Yet the mortality for NHBs was 37% higher for this disease (Fig. 20). Black women in the United States have a higher prevalence of mammography screening than do white women. Knight et al. [55] has presented evidence that higher levels of vitamin D intake and sun exposure, particularly during the period of

Table 2 CA by site and treatment arm from years 2–4 (Bibuld D from [49])

	Placebo (266)	Ca++ (416)	Ca+++ Vit D (403)
Breast	7	6	4
Colon	2	0	0
Lung	3	2	1
Hematopoietic	4	4	2
Uterus	0	1	0
Other	2	2	1
Total (%)	18 (6.8)	15 (3.7)	8 (2.0)

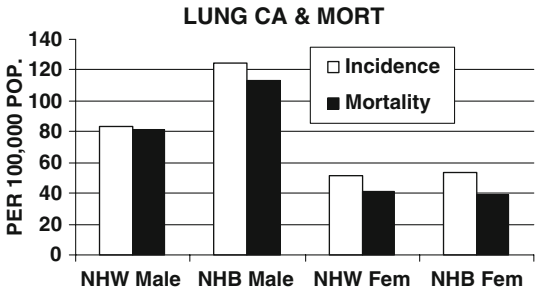

Fig. 18 Lung CA and MORT (Bibuld D, from [46])

Table 3 Serum 25(OH)D and mortality among 447 patients with early stage NSCLC (Bibuld D from [50])

	Lowest quartile RR	Highest quartile RR	Higher level and intake by medians—RR
Overall survival	1	0.74	0.64
Stage IB–IIB	1	0.45	0.67

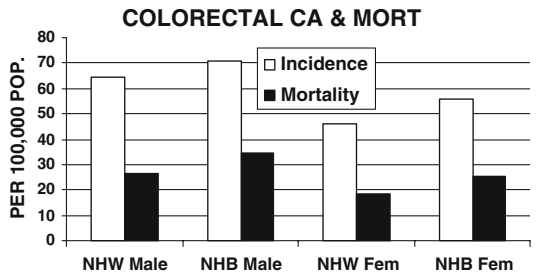

Fig. 19 Colorectal CA and MORT (Bibuld D, from [46])

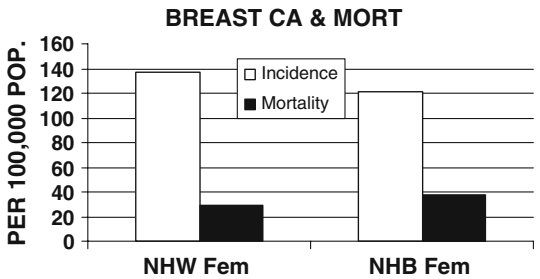

Fig. 20 Breast CA and MORT (Bibuld D, from [46])

adolescent breast development is associated with decreased later incidence of breast cancer. Lappe et al. [49] found a 1.0% incidence of breast cancer in the group supplemented with vitamin D, compared to a 2.6% incidence in women receiving placebo from the second to fourth year of that study. Neuhouser et al. [56], in a multiethnic study of breast cancer survivors, found that the stage of disease was independently associated with serum 25(OH)D levels with lower levels associated with more advanced disease.

Prostate cancer occurs 59% more frequently in NHB (275.3 per 100,000) than NHW males 172.9 per 10000) in the US. Its mortality rate is 2.4 times higher (75.1 vs. 32.9 per 100,000) in NHBs than NHWs (Fig. 21) [43]. In Trinidad the age-adjusted mortality rate from prostate cancer (32.3 per 100,000) was about the same as for NHWs in the US (32.9 per 100,000) [57]. Mauritius, a nation of very dark-skinned people located just north of Senegal at the western edge of the Sahara desert, had an age-adjusted prostate cancer mortality rate of 7.3 per 100,000 (Fig. 22).

A nested control study in Finland [58] based on 13 year follow-up of 19,000 middle aged men who were free of prostate cancer at baseline found a RR of 1.7 for men entering the study with serum 25(OH)D levels <16 ng/ml (the mean in that population) compared with those who had ≥16 ng/ml. However, the RR for males <52 years with serum 25(OH)D <16 ng/ml was 2.5, along with an RR of 6.3 for metastatic disease. John et al. [59] found large reductions in the incidence of advanced cancer with high

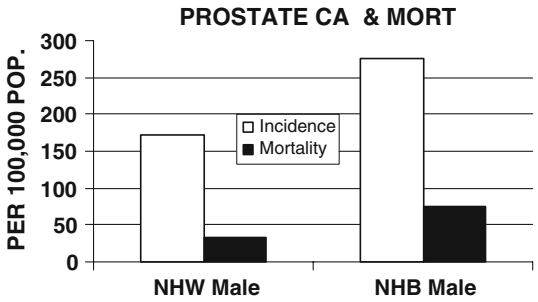

Fig. 21 Prostrate CA and MORT (Bibuld D, from [46])

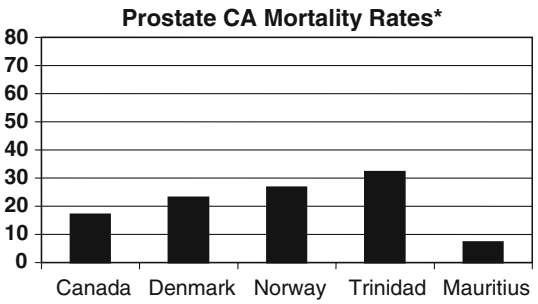

Fig. 22 Prostrate CA mortality rates* (Bibuld D, from Survival, Epidemiology and End Results Program, 1978–1999, Division of CA Control and Pop. Sciences, NCI)

recreational and occupational sun exposure in NHWs, as have others. Li et al. [60] found among US physicians that those whose median serum levels of 25(OH)D fell below 32 ng/ml for the summer and 25 ng/ml in the winter had significantly increased risk of total and aggressive prostate cancer. This was particularly the case if they had a relatively common vitamin D receptor polymorphism. However, among men with 25(OH)D levels above those means in summer and winter the genotype associated with that polymorphism was no longer associated with increased risk, and was related to a 60–70% lower risk of total and aggressive prostate cancer compared to men with levels of 25(OH)D below those medians.

Total Mortality

Figure 1 graphs the average life expectancy at birth by race and sex from 1970 to 2003. Despite the gradual increase in life expectancy over this period the gap between black and white life expectancy in the US remains remarkably constant. Recent studies implicate the gap in serum 25(OH)D levels between the population groups as being a significant contributor to this disparity; sufficient perhaps to account for the entirety of this disparity.

Autier and Gandini [61] conducted a meta-analysis of all available medical literature published up to November 2006 of randomized controlled trials in which vitamin D was given for any health condition and death was a reported outcome. A search of the PubMed, ISI Web of Science, EMBASE, and Cochrane databases revealed 18 such trials. The trials encompassed 57,311 participants and 4777 deaths. The mean trial period was 5.7 years, with individual trials running from 6 to 84 months. The mean vitamin D supplementation dose was 528 IU daily, with a range of from 300 to 2000 IU daily. The analysis showed that patients receiving vitamin D supplementation in the trials had 7% less mortality than control subjects. In trials lasting at least 3 years vitamin D supplementation resulted in 8% fewer deaths. Where calcium supplementation was given with vitamin D, treated subjects had 7% less mortality, but in trials in which vitamin D was the sole supplement given subjects had 9% less mortality. In trials that were placebo controlled, vitamin D supplementation resulted in 8% less mortality.

Dobnig et al. [40] reported a prospective cohort study of 3258 consecutive patients having coronary angiography, looking at the relationship of 25(OH)D and $1,25(OH)_2D$ levels to all-cause and cardiovascular mortality. Comparing patients by quartiles of 25(OH)D they found that patients in the lowest quartile (median serum 25(OH)D of 7.6 ng/ml) had a multivariate adjusted RR of 2.08 for all-cause mortality compared to the highest quartile (median 28.4 ng/ml).

The RR of mortality for the next to lowest quartile (mean 25[OH]D of 13.3 ng/ml) was 1.53. Serum $1,25(OH)_2D$ levels were independently associated with all-cause (and cardiovascular) mortality, and the study found only weak correlation between serum 25(OH)D and $1,25(OH)_2D$ levels. The relative impact of quartile of serum $1,25(OH)_2D$ level on mortality did not approach that of 25(OH)D level above the lowest quartiles.

Melamed et al. [41] reviewed NHANES III data of 13,331 adults ≥20 years. The 25(OH)D levels were collected from 1988 to 1994, and individuals were followed for mortality through 2000. Mortality rates were computed by quartile of 25(OH)D level. Those in the highest quartile had >32 ng/ml and those in the lowest had <17.8 ng/ml. A total of 43.5% of NHWs fell into the highest quartile, while only 7.8% of NHBs were represented therein. A total of 9.5% of NHWs were found in the lowest quartile, along with 50.3% of blacks. Without adjustment those in the lowest quartile of vitamin D had a 78% increased risk of all-cause mortality than those in the highest quartile. After adjustment for age, sex, race, and season the mortality rate for the lowest quartile was 52% higher. After further adjustment for hypertension, CVD history, diabetes, smoking, HDL cholesterol, total cholesterol, use of anti-cholesterol medications, glomerular filtration rate, serum albumin, albumin creatinine ratio, C-reactive protein, body mass index, physical activity, vitamin D supplementation, and low socioeconomic status mortality remained 26% higher in the lowest quartile of serum 25(OH)D.

Diabetes

According to The Office of Minority Health (OMH) [62], a department of HHS, "African Americans are 2.2 times as likely to have diabetes as Whites." As reported on its website in November 2008 "Hispanics are 1.5 times as likely to have diabetes as Whites." They also noted that "American Indian and Alaskan Natives are 2.3 times as likely as non-Hispanic Whites of similar age to have diabetes." Age-adjusted death rates from diabetes mellitus have historically been highest in NHBs of the population groups mentioned. In 2005 the relative age-adjusted risk of mortality for diabetes for Black, AI/AN, Hispanic, and Whites were 2.2, 1.9, 1.6, and 1.0, respectively [63].

The positive association of serum vitamin D levels with insulin sensitivity, insulin secretion from pancreatic β-islet cells, and glucose tolerance in both animals and humans has been well established [64–66]. Vitamin D deficiency has also been associated with glucose intolerance and Type 2 diabetes [7, 64, 67, 68]. Vitamin D supplementation has been shown to improve these measures in diabetic patients [69–71].

These studies have not been detailed enough to determine the magnitude of impact of either serum 25(OH)D level or supplementation on the incidence or severity of this disease.

Tuberculosis

Steele et al. [72] in a review for the CDC reports that "US-born blacks have consistently had tuberculosis rates eight times higher than US-born whites." In 2004 45% of US-born persons with tuberculosis were black.

Vitamin D has been shown to have a positive effect on macrophage function and to inhibit intracellular growth of tuberculosis and enhance killing of mycobacterium tuberculosis (MTB). The 25(OH)D deficiency has been shown to be associated with active tuberculosis. It has been shown that sera from African-American individuals, low in 25-hydroxyvitamin D, were inefficient in producing cathelicidin, the antimicrobial peptide (AMP) responsible for enhancement of macrophage killing of MTB. It was also shown that restoring 25(OH)D in the sera of those same African-American individuals to physiologic range restored the killing ability of macrophages in that sera [73–75].

HIV/AIDS

Continuing a historical pattern, the CDC defined black population had the highest HIV/AIDS infection rate in 2004, with 69.3 cases per 100,000 population. Hispanics had the second highest rate at 26.6 cases, followed by American Indians, whites and Asians with 10.2, 8.2, and 6.5 cases per 100,000 population, respectively [72].

While it is beyond the scope of this chapter to explore the curious history and epidemiology of HIV/AIDS infection in human beings, there are suggestions that vitamin D status may play an important role in defense against this virus. There has been little research to date in this area, but there is scientific basis for promise of positive results. Cannell [76] has pointed out that HIV has a lipoprotein coat, and viruses with lipoprotein coats are susceptible to attack by AMPs. The 1,25(OH)D has been shown to induce production of AMPs such as cathelicidin and defensins [77]. Defensins have been shown to inhibit HIV and suppress HIV infection [78–80].

Observation suggests that the spread of AIDs in subtropical southern Africa has been more of a problem than in tropical Sub Saharan Africa where it appears to have been stable for many years. In the United States the prevalence of HIV/AIDS has been historically much higher in the northeast compared to other areas of the country, and the

prevalence of HIV/AIDS in the west well below the mean for US despite the early loci of AIDS in Los Angeles and San Francisco and the higher black population rate in the South [72]. Disparities in serum 25(OH)D levels could be a contributing factor to this distribution.

Similarly, despite the identification of Haitian natal origin as a major risk factor for HIV/AIDS early in the epidemic, Haiti, the poorest country in the western hemisphere, is not known for having a significant HIV problem, nor are other Caribbean countries afflicted in a major way. Observation at Mattapan Community Health Center (Unpublished data from Mattapan Community Health Center, observed by author Bibuld D), which serves a proportionately large concentration of Haitian immigrants and transients, has shown vitamin D levels in transients and recent émigrés from Haiti and other Caribbean countries to be much higher than in residents of the US. Mattapan, which has the largest Haitian community in Massachusetts, as well as being 83% black, has an HIV incidence rate that is 20% higher than Boston as a whole. Boston's Black residents overall had an incidence rate of HIV 39% higher than Boston's rate [81].

Conclusion

A lot of time, money, and research have been given to explain disparities in health outcome between so-called racial subpopulations in the United States. These disparities have been especially confusing given evidence that groups of immigrants moving to the United States from other parts of the world have appeared to assume the health characteristics of the traditional majority population of the US within one to two generations.

It now appears that the bulk of these health disparities can be attributed to the disparity in vitamin D production related to the degree of melanin pigmentation and sun exposure in individual human beings. This evidence based theory, though contrary to prevailing thought that unequal access to the technology of healthcare is at the root of health disparities, is entirely consistent with the history of public health science: that environmental factors are the key effectors of human health.

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