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Does 'imprinting' with low prenatal vitamin D contribute to the risk of various adult disorders?

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Summary Hypovitaminosis D is a candidate risk-modifying factor for a diverse range of disorders apart from rickets and osteoporosis. Based on epidemiology, and on in vitro and animal experiment, vitamin D has been linked to multiple sclerosis, certain cancers (prostate, breast and colorectal), insulin-dependent diabetes mellitus and schizophrenia. I hypothesise that low pre- and perinatal vitamin D levels imprint on the functional characteristics of various tissues throughout the body, leaving the affected individual at increased risk of developing a range of adult-onset disorders. The hypothesis draws from recent advances in our understanding of the early origin of adult disease and proposes a 'critical window' during which vitamin D levels may have a persisting impact on adult health outcomes. Methods to test the hypothesis are outlined. If correct, the hypothesis has important implications for public health. Careful attention to maternal vitamin D status could translate into diverse improvements in health outcomes for the following generation. © 2001 Harcourt Publishers Ltd

PRE- AND PERINATAL EXPOSURES AND METABOLIC IMPRINTING

The hypothesis that environmental factors may 'imprint' on the fetus and contribute to adult health has been stimulated by the work of Barker and colleagues (1). Metabolic imprinting has two key features; (a) there is a critical window during fetal development or early life when the fetus is particularly sensitive to exposures; and (b) the exposure leads to changes that persist throughout adulthood. Waterland and Garza (2) have recently proposed several mechanisms for metabolic imprinting. Apart from induced variations in organ structure (e.g. vascularization and/or innervation during organogenesis) and alterations in cell numbers (e.g. changes in neuronal count/density after prenatal malnutrition), metabolic imprinting may be mediated by clonal selection and metabolic differentiation. Clonal selection may have long-lasting effects if early nutritional or hormonal exposures differentially advantage certain cell lines: the more numerous facilitated daughter cells may have persisting consequences for the adult organism. Imprinting may also operate by 'metabolic differentiation': the process of cells acquiring a stable quantitative pattern of basal and inducible gene expression. These mechanisms may relate to enzymes, hormones and their receptors and other components of cellular molecular biology. Metabolic differentiation includes epigenetic mechanisms related to chromatin structure, DNA methylation, and autoregulatory patterns of DNA binding protein.

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HEALTH AND VITAMIN D: CLUES FROM BIOLOGY AND EPIDEMIOLOGY

Evidence linking vitamin D and various disorders is based on in vitro, animal and ecological-level research. None of these features in isolation would be sufficient 'proof' that vitamin D is involved in causal pathways; however, the coherence of the data suggests that low vitamin D is a

candidate risk-modifying factor for a range of diseases other than rickets and osteoporosis. The table displays some of the evidence linking vitamin D and diseases such as multiple sclerosis, breast cancer, prostate cancer, colorectal cancer, insulin dependent diabetes and schizophrenia. The epidemiological similarities between some of these diseases have already been noted for prostate cancer and multiple sclerosis (3), schizophrenia and multiple sclerosis (4,5), and colorectal cancer and multiple sclerosis (6). The evidence linking vitamin D and these disorders can be summarised under several headings:

(1) In vitro and animal experiments. Vitamin D can ameliorate the expression of animal models of multiple sclerosis (7) and diabetes mellitus (8). Vitamin D can lead to increased differentiation in cell cultures derived from prostate (9), breast (10) and colorectal cancer (11).

(2) Incidence/prevalence associations with latitude. Many diseases have gradients in incidence, prevalence and outcome that are correlated with latitude. Latitude acts as a risk indicator (or proxy) for the population distribution of serum vitamin D levels. A negative correlation between latitude and disease incidence is found for disorders such as multiple sclerosis (12,13), breast cancer (14), prostate cancer (15), colorectal cancer (6), insulin dependent diabetes mellitus (16)(17) and schizophrenia (18,19).

(3) Ultraviolet B radiation (UVB). The geographical distribution of several diseases has been linked to measures related to the availability of UVB. This exposure is strongly correlated with latitude and vitamin D levels (20). Diseases that have been associated with measures related to sunshine include multiple sclerosis (12), breast cancer (21,22), prostrate cancer (15,23), colorectal cancer (14,23,24), and insulin dependent diabetes mellitus (25). The between-year fluctuations in schizophrenia birth rates have also been linked to measures of sunshine (26).

(4) Season of birth. The amount of ultraviolet radiation fluctuates across the seasons such that individuals born in winter and early spring tend to be exposed to lower levels of vitamin D than those born in other months. Disorders that have an excess of winter/spring births suggest that early life exposures to low vitamin D may be a risk-modifying exposure. There is robust evidence from the Northern Hemisphere showing that schizophrenia has seasonality of birth (27), and similar but weaker evidence for multiple sclerosis (28).

(5) Urban-rural gradient. Urban residence is associated with higher prevalence of hypovitaminosis D (20). Diseases that have urban excess include breast cancer (29) and schizophrenia (30). Urban residence is also strongly linked to air pollution, a local factor that influences the availability of UVB. Colorectal and breast cancer (31) have been associated with air pollution.

(6) Migrant studies. The offspring of dark-skinned migrants to cold climates are prone to low vitamin D. Those with dark skin require slightly longer exposure to UVB in order to produce previtamin D, and their behaviour (e.g. dress, outdoor activity, diet) may amplify the risk of hypovitaminosis D. Multiple sclerosis has a lower incidence in first generation Asian migrants to the UK than second generation migrants (those born in the UK) (32, 48–50). There is a significantly higher rate of schizophrenia in the second but not the first generation of Afro-Caribbeans in the UK (30).

(7) Oral Vitamin D intake. Apart from sunshine exposure, Vitamin D can be derived from certain foods in the diet, cod liver oil intake and vitamin supplementation. Case-control and cohort studies have found links between low oral vitamin D intake and increased risk of prostate and colorectal cancer (33,34) and insulin-dependent diabetes mellitus (35). (Table 1)

HYPOTHESIS

While the incidence of rickets has declined markedly over the last century, hypovitaminosis D is still relatively common in developed and developing countries (36,37). A large US survey reported that 12% of women aged 20 to 39 (peak ages for child-bearing) had serum 25-hydroxyvitamin D_3 levels below the threshold defined for vitamin D deficiency (≤ 15 ng/ml) (38). Pregnant women are at risk of hypovitaminosis D because of the increased needs of the fetus and the potential for these women to reduce their outdoor activity, leading to diminished supply of vitamin D (39,40).

I propose that low pre- and perinatal vitamin D 'imprints' on a range of tissues, leaving the affected individual at increased risk of developing a range of disorders including osteoporosis, multiple sclerosis, breast cancer, prostate cancer, colorectal cancer, insulin-dependent diabetes mellitus and schizophrenia. The early life exposure contributes to risk status in addition to other factors such as genetic susceptibility and adult exposures (including hypovitaminosis during adult life). With respect to the putative mechanisms of metabolic imprinting, it is proposed that vitamin D mediated alterations in neuronal proliferation, differentiation, migration and apoptosis may be implicated in schizophrenia. Vitamin D receptors have been found in differentiating zones of the central

Table 1 Evidence linking vitamin D and selected disorders

	Epidemiological clues linking diseases to vitamin D and ultraviolet radiation				
	Duration of sunshine	**Latitude**	**Migrant studies**	**Season of birth Urban-rural gradient Other risk indicators**	**Biological factors related to vitamin D**
Multiple sclerosis	Increased risk associated with low sunshine in US veterans (12)	Increased prevalence at higher latitudes (12, 13)	Increased risk from 1st to 2nd generation migrants to higher latitudes (48) MS rare in Afro-Caribbean migrants to the UK, but rates are similar to Caucasians in their offspring (second generation (32,49,50)	Excess births in Spring – 2nd and 3rd trimester exposure to low vitamin D (28)	Vit D reverses the most commonly used animal model of MS (7)
Breast cancer	Negative correlation with sunshine (21, 22)	Increased incidence at higher latitudes (14)		Strong association between sunshine and Breast cancer in urban versus rural settings (29) Increased risk associated with air pollution in Canada (31)	Vitamin D increases differentiation in breast cancer cell lines in vitro (10)
Prostate cancer	Association between high UV radiation and reduced risk (15,23)	Negative correlation with latitude (in USA) (15)	Increased risk from 1st to 2nd generation migrants (Japanese migrants to US) (15) High rates in African Americans in contrast to low rates in black men in African (15)		Vitamin D increases differentiation in prostate cancer cell lines (9)
Colorectal cancer	Inverse assocation between mean daily solar radiation and age-adjusted colon cancer death rates (14,23,24)	Increased incidence at higher latitudes (6)		Cohort studies show that lower vitamin D and calcium intake was associated with higher rates of colorectal cancer (34) Increased risk associated with air pollution in Canada (31) Swedish case-control study reported trend for reduced colorectal cancer with higher vitamin D in diet (33)	1,25 dihydroxy inhibits proliferation of colon cancer cell lines increases differentiation (11)
Insulin dependent diabetes	Swedish study reported a link incidence and sunshine (25)	Higher rates at higher latitudes in Europe and in global comparisons (16, 17)		European multi-centre (7 sites) case-control study reported an association between vitamin D supplementation and reduced odds ratio for IDDMS (35) Age of onset lower at higher latitudes in Sweden (25)	Vitamin D prevents insulitis in nonobese diabetic (NOD) mouse model of human auto-immune (Type 1) diabetes (51)
Schizophrenia (18, 19)	Increased birth rates (males only) associated with duration of sunshine Earlier age of onset associated with duration of sunshine	Increased prevalence at higher latitudes Worse outcome at higher latitudes Increased season of birth at higher latitudes	Increase rates of schizophrenia in second generation Afro-Caribbean migrants to the UK	Season of birth effect (excess births in winter/spring) Urban birth is a risk factor for schizophrenia	

nervous system of the rat embryo (41) and vitamin D is a potent inducer of Nerve Growth Factor synthesis (42). Factors related to clonal selection and metabolic differentiation may be particularly important in the vitamin D related cancers (breast, prostate, colorectal), multiple sclerosis and insulin-dependent diabetes mellitus.

This hypothesis gains biological plausibility from the demonstration of persisting alterations in cellular responsivity and organ differentiation after early-life exposure to vitamin D (43,44).

Interestingly, low prenatal vitamin D has recently been implicated in the pathogenesis of syndrome 'X' (increased insulin resistance, hyperlipidaemia, hypertension, central obesity, increased fibrinogen and increased risk of non-insulin dependent diabetes mellitus) (45). It is proposed that low prenatal vitamin D might contribute to low birth weight and program aspects of pancreatic islet beta cell function. These features would then amplify the consequences of adult hypovitaminosis, thus leading to increased risk of syndrome 'X'. A diverse range of evidence suggests that low prenatal vitamin D is a candidate exposure for a range of adverse adult health outcomes.

TESTING THE HYPOTHESIS

One could measure vitamin D levels in a large cohort of pregnant women, and then follow-up their offspring for several decades in order to search for a dose-response relationship (a biological gradient) between low Vitamin D and increased risk of the candidate disorders. If sera from pregnant women and/or cord blood from their offspring were 'banked down' during past decades, maternal vitamin D levels and rates of candidate disorders in the offspring could be examined.

From an ecological perspective, 'natural' and opportunistic experiments that impact on Vitamin D may provide exposed and non-exposed cohorts for birthrate comparisons (e.g. famine, clusters of rickets, the introduction of vitamin D supplementation). Between-year fluctuations in birth rates of candidate disorders could be examined for associations with duration of sunshine. For example, geographically-defined birth cohorts (born over several decades) could be divided according to quartiles of perinatal sunshine exposure, and rates of diseases could be compared between these quartiles. It would be predicted, for example, that rates of schizophrenia, diabetes mellitus, multiple sclerosis, breast cancer, prostate cancer and colorectal cancer would be higher in those born during those periods with less sunshine. The hypothesis predicts that vitamin D related disorders will cosegregate in birth cohorts that have been exposed to low prenatal vitamin D. If possible, case-control studies of candidate disorders should ask mothers about prenatal sunshine behaviour, and vitamin D intake.

If the hypothesis gains support then a randomized controlled trial of vitamin D supplementation during pregnancy would be indicated; however, the assessment of outcomes would require several decades of observations. Animal experiments could examine the impact on low prenatal vitamin D on a range of health outcomes; however, not all human diseases have robust animal models. The hypothesis also suggests new directions for genetic research: as the hypothesis implicates a prenatal vitamin D deficiency, maternal genes related to vitamin D metabolism warrant consideration in addition to those of the affected offspring.

IMPLICATIONS FOR PUBLIC HEALTH

Programs that aim to reduce the prevalence of hypovitaminosis D in pregnant women could translate into a lower incidence of candidate disorders in their offspring. Just as folate supplementation has been shown to reduce the incidence of neural tube defects (46), attention to vitamin D status (diet, sunlight exposure) could reduce the burden of a range of diseases. The population attributable fraction of a particular disease that could be linked to low prenatal vitamin D is not clear. In addition, the specificity of the outcomes is weak. However, this feature is a distinct advantage from the public health perspective. If an intervention designed to reduce one particular exposure translates into reduced incidence of several common disorders, then these exposures are deemed more attractive candidates for preventive medicine (47).

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