Metabolic syndrome: A review of the role of vitamin D in mediating susceptibility and outcome

Richard C Strange, Kate E Shipman, Sudarshan Ramachandran

Abstract

Despite the well-recognised role of vitamin D in a wide range of physiological processes, hypovitaminosis is common worldwide (prevalence 30%-50%) presumably arising from inadequate exposure to ultraviolet radiation and insufficient consumption. While generally not at the very low levels associated with rickets, hypovitaminosis D has been implicated in various very different, pathophysiological processes. These include putative effects on the pathogenesis of neoplastic change, inflammatory and demyelinating conditions, cardiovascular disease (CVD) and diabetes. This review focuses on the association between hypovitaminosis D and the metabolic syndrome as well as its component characteristics which are central obesity, glucose homeostasis, insulin resistance, hypertension and atherogenic dyslipidaemia. We also consider the effects of hypovitaminosis D on outcomes associated with the metabolic syndrome such as CVD, diabetes and non-alcoholic fatty liver disease. We structure this review into 3 distinct sections; the metabolic syndrome, vitamin D biochemistry and the putative association between hypovitaminosis D, the metabolic syndrome and cardiovascular risk.

Key words: Vitamin D; Hypovitaminosis D; Metabolic syndrome; Type 2 diabetes mellitus; Insulin resistance; Cardiovascular disease; Atherogenic dyslipidaemia; Hypertension; Non-alcoholic fatty liver disease

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.
levels of hypovitaminosis and the benefits of vitamin replacement are unknown. However, unravelling the association between hypovitaminosis and the syndrome is warranted as even a modest decrease in CVD risk would confer substantial benefits.


INTRODUCTION

Much research over the last 30 years has shown that the pleiotropic actions of 1, 25 dihydroxy-vitamin D[1,25(OH)2D] are central to cell, organ and organism homeostasis. Thus, along with its historic functions as a mediator of calcium and bone metabolism, 1,25(OH)2D has effects on a wide range of physiological processes. It is perhaps surprising, given its perceived importance to public health, to find that hypovitaminosis D is common worldwide (prevalence 30%-50%). This deficiency presumably arises from failure to firstly, ensure adequate exposure to ultraviolet radiation (UVR) because of skin cancer fears and secondly, consume food with sufficient levels of the vitamin. Vitamin D status is identified by low serum levels of biologically inactive 25-hydroxylated vitamin D [25(OH)D]. While generally not at the very low levels associated with rickets, hypovitaminosis D has been implicated in various very different, pathophysiological processes. These include a putative effect on the development of neoplastic, inflammatory, demyelinating, cardiovascular and diabetic conditions. While the impact of hypovitaminosis D on health remains unclear, accumulating data indicates it confers increased disease risk and in some cases worse outcome.

In the context of this review, the finding that hypovitaminosis D is associated with impaired glucose homeostasis is of particular interest. A meta-analysis of 28 studies demonstrated that higher serum 25(OH)D levels were associated with a 55% reduction in diabetes, a 51% decreased risk of the metabolic syndrome and a 33% lower risk of cardiovascular disease (CVD)[1]. Further, treatment with vitamin D supplements over 2 mo improved fasting glucose levels and insulin resistance homeostasis model assessment for insulin resistance (HOMA-IR) in 100 patients with type 2 diabetes[2]. It is suggested that the mechanism for this latter finding involves improved sensitivity of target tissues such as the liver, muscle and bone to insulin as well as enhanced beta cell function. Given that many risk factors for CVD are clustered in the highly prevalent metabolic syndrome, which is characterised by insulin resistance and abdominal obesity, it is reasonable to speculate a significant role for the vitamin in the development of the syndrome and its sequelae of diabetes and CVD.

Strange RC et al. Vitamin D and the metabolic syndrome

In this review we focus on the association between hypovitaminosis D and the metabolic syndrome and how this may contribute to increased CVD risk. We present 3 sections describing firstly, the metabolic syndrome, secondly, vitamin D biochemistry and thirdly, the putative association between hypovitaminosis D, the syndrome and CVD risk.

METABOLIC SYNDROME: HOW IT WAS IDENTIFIED

The relationship between sensitivity to insulin, obesity and glucose homeostasis was first observed by the Swedish physician Eskil Kylin[3]. He described a syndrome comprising hyperglycaemia, hypertension and hyperuricaemia and suggested insulin resistance as a possible causative factor[3]. Subsequently Himsworth et al[4] laid the foundations for the classification of type 1 and 2 diabetes by showing that while some patients were insulin sensitive (younger, normal weight and blood pressure) others are insulin insensitive (older, more obese, hypertensive and atherosclerotic). Vague, in studies on gender-related obesity patterns described android obesity (now termed central obesity and linked with diabetes and atherosclerosis) and suggested a hormonal aetiology with over-activity of the pituitary-adrenal axis playing a key role[5].

Such observations were brought together by Reaven[6] in his Bantering Lecture to the American Diabetes Association in 1988. He termed the combination of hypertension, dyslipidaemia and glucose intolerance as syndrome X and proposed that this mix of phenotypes provided a pathophysiological basis for atherosclerosis. Obesity, was also seen as a further essential component and following a number of iterations (dyslipidaemic hypertension, deadly quartet, insulin resistance, hazardous waist), the combination of phenotypes is now termed the metabolic syndrome[7] with the International Classification of Disease code of 277[8].

Classification of the metabolic syndrome

Various groups including the World Health Organisation[9], European Group for the Study of Insulin Resistance[7], American Association of Clinical Endocrinologists[10], National Cholesterol Education Program - Adult Treatment Panel III[11] and, more recently, the International Diabetes Federation (IDF)[12,13] have provided definitions of the metabolic syndrome (Table 1). While all are based on the characteristics presented by Reaven[6], there are various inclusion thresholds. A form of consensus was arrived at in 2009[14] with the IDF, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis and the International Association for the Study of Obesity agreeing on threshold levels that were similar to those originally proposed by the IDF. Guidelines for classifying metabolic syndrome in children over 10 years of age were also issued[15] and population and gender specific
Table 1  Thresholds defining the metabolic syndrome issued by individual organisations

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma insulin &gt; 75th percentile or lowered insulin sensitivity</td>
<td>IGT, IFG, T2DM</td>
<td>Plasma</td>
<td>IGT or IFG plus any of the following based on clinical judgement</td>
<td>See below</td>
<td>≥ 94 M</td>
<td>&gt; 90th percentile Plus 2 of the following</td>
</tr>
<tr>
<td>Plus 2 of the following</td>
<td></td>
<td>≥ 102 M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europoid waist circumference (cm)</td>
<td>W:H &gt; 0.90 M</td>
<td>W:H &gt; 0.85 F or BMI &gt; 30 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W:H &gt; 0.85 F or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride [mg/dL (mmol/L)]</td>
<td>&gt; 150 (1.7)</td>
<td>&gt; 150 (1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL [mg/dL (mmol/L)]</td>
<td>&lt; 35 (0.91) M</td>
<td>&lt; 35 (0.91) M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 39 (1.01) F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>≥ 140/90</td>
<td>≥ 140/90 or on treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100 (5.6) (Grundy) or diabetes</td>
<td>IGT or IFG</td>
<td>IGT or IFG (but not diabetes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Microalbuminuria</td>
<td>Other features of IR¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR &gt; 30 mg/g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Includes polycystic ovary syndrome, family history or ethnic group susceptible to type 2 diabetes, sedentary lifestyle and advancing age. ACR: Albumin creatinine ratio; BMI: Body mass index; DBP: Diastolic blood pressure; F: Female; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; IR: Insulin resistance; SBP: Systolic blood pressure; M: Male; T2DM: Type 2 diabetes mellitus; W:H: Waist to hip ratio; WHO: World Health Organization; HDL: High density lipoprotein; IDF: International Diabetes Federation; EGIR: European Group for the Study of Insulin Resistance; NCEP: National Cholesterol Education Program; AACE: American Association of Clinical Endocrinologists; BP: Blood pressure; IR: Insulin resistance.

waist circumference thresholds were published to define central obesity¹³. The prevalence for the metabolic syndrome varies between countries. Based on the IDF classification a 40% prevalence in the United States has been reported⁶⁶.

Is there a clinical value in identifying the metabolic syndrome? It is not surprising, given the presence of known risk factors, to find that the metabolic syndrome confers an approximately two-fold increased relative risk of CVD¹⁷. However, it is important to determine whether this impact is the effect of the metabolic syndrome (added risk due to a clustering of risk factors) or just the sum of its defining phenotypes. Studies using different CVD endpoints indicate the latter is the case. For example, Eddy et al¹⁸ used data from NHANES III (third national health and nutrition survey) to simulate a population matching that of the United States, estimated its metabolic syndrome prevalence (using the various definitions) and associated this with CVD. While the number of individuals identified by the various metabolic syndrome classifications differed, they reported that fasting glucose levels > 110 mg/dL (6.1 mmol/L) were a better predictor of CVD than the presence of the metabolic syndrome classified by any of the definitions¹⁸. Further, using change in atheroma volume as an endpoint, Bayturhan et al¹⁹ reviewed 3459 patients enrolled in 7 trials that used intravascular ultrasonography to measure plaque progression. While the metabolic syndrome was significantly associated [odds ratio (OR) = 1.29, 95%CI: 1.09-1.53] with increased atheroma volume, the relationship was not significant (OR = 1.04, 95%CI: 0.79-1.37) when adjusted for its individual components; serum triglycerides ≥ 150 mg/dL (1.7 mmol/L), body mass index (BMI) ≥ 30 kg/m², high density lipoprotein cholesterol (HDL-C) < 40 mg/dL (1.0 mmol/L) in men or < 50 mg/dL (1.3 mmol/L) in women, blood pressure ≥ 135/85 mmHg or treatment of hypertension¹⁹. In this multifactorial model, only serum triglyceride concentrations (≥ 150 mg/dL) remained significantly associated with plaque progression¹⁹.

These findings (and others) question the clinical value of identifying the metabolic syndrome in patients. Indeed, the identification is dependent on the thresholds of each of the contributing factors. Thus, for example, if age-related thresholds were used there would be a marked change in the numbers of affected individuals. While in theory its identification does not appear to add anything to prognosis in an individual patient, we and others²⁰ argue that it has clinical value. As the metabolic syndrome is based on related and modifiable CVD risk factors, its identification encourages a holistic approach rather than a focus on the individual aspects (glycaemia, dyslipidaemia, weight reduction and blood pressure management) of the patients’ condition. It therefore, has value in encouraging the clinician to address CVD risk using a multifactorial approach. It is also arguably useful in a research setting when considering the role of possible risk factors.

We also believe it is important to consider the
metabolic syndrome as a heterogeneous entity. Indeed, in patients with the syndrome, we have shown that following treatment with statins and fibrates, outcomes can vary considerably indicating the presence of subgroups both known (gender, baseline lipids, and concurrent therapy) and unknown[21-24].

**Metabolic syndrome - putative pathway to CVD:**

While it is accepted that central obesity and insulin resistance are core drivers of the metabolic syndrome, the timescale and inter-relationships between these and other factors that lead to an individual being classified with the syndrome and the consequent increased risk of CVD remain unclear[25-27]. Clearly, while obesity and insulin resistance are common in adults worldwide they are rare in childhood indicating that environmental factors interacting with a genetic predisposition drive the development of the syndrome from birth through childhood to its identification in adulthood. Once an individual develops the metabolic syndrome, the combination of risk factors leads to an increased risk of CVD (Figure 1).

Obesity is a recognised risk factor associated with mortality, this probably due to the link between obesity and risk of developing diabetes, hypertension, atherogenic dyslipidaemia and CVD[28]. However, the National Health and Nutrition Examination Survey (NHANES) indicated that individuals with a BMI between 30 and 35 kg/m² demonstrated only a modest increase in mortality compared to those with BMI 18.5-25 kg/m²[27,29]. These findings suggest the presence of a subgroup of obese individuals who are not at high risk of metabolic disturbances or increased mortality. Their presence may be a reason for the relatively modest increase in overall mortality in obese subjects. It has been speculated that the link between obesity and CVD may be via insulin resistance[27]. Individuals with high insulin sensitivity and not fulfilling the ATP III metabolic syndrome criteria are considered to be a “metabolically healthy obese” group[29].

The concept that not all obesity is bad in the context of developing CVD is interesting. Abdominal obesity, visceral as opposed to subcutaneous fat, appears to be critical in the development of insulin resistance[30]. Abdominal adipose tissue was initially considered an inert storage depot for triglycerides (glycerol and fatty acids). The current view however, is that it is also an active endocrine organ. Intra-abdominal obesity, a classifying characteristic of the metabolic syndrome promotes insulin resistance (the reverse of insulin sensitivity), perhaps by secreting metabolically active substances (adipokines) and making available an increased quantity of free fatty acids[30,31].

Insulin resistance, the other key factor in the metabolic syndrome, is defined as a condition where greater than normal levels of the peptide are needed to clear a glucose load (and effect its other metabolic actions). Thus, for a given blood glucose level the amount of insulin secreted is high. Impairment of sensitivity appears to be a contributing factor to all of the features of the metabolic syndrome in addition to having a direct causative role in the pathogenesis of type 2 diabetes. It can be considered a pre-diabetic state in non-diabetic patients, conferring a 5 fold increased risk of developing diabetes[29]. Insulin resistance has also been demonstrated to be associated with hypertension, atherogenic dyslipidaemia and higher amounts of the atherogenic small dense low density lipoprotein cholesterol (LDL-C), features associated with the metabolic syndrome[20,33].

Thus, in addition to weight reduction measures, reducing insulin resistance, a feature that may be an intermediate factor linking obesity with morbidity and mortality, must be addressed in patients with the metabolic syndrome. Apart from abdominal obesity there are other factors that may modify insulin resistance. Physical fitness (as measured by aerobic capacity) has been seen to increase insulin sensitivity[34].

**VITAMIN D BIOCHEMISTRY**

Vitamin D, in addition to its role in calcium and bone metabolism, has pleiotrophic effects in many cell types in many life forms. These include a potential role in the actions of insulin and development of obesity (Figure 1). Thus, not surprisingly hypovitaminosis D has been linked with hypertension, atherogenic dyslipidaemia and increased CVD risk (Figure 1). An association has
compared with that of a young adult has approximately 25% of the 7-dehydrocholesterol is marked; for example, the skin of a 70-year-old subject in reduced capacity to synthesise vitamin D. 7-dehydrocholesterol falls with increasing age resulting in reduced capacity to synthesize vitamin D. This effect is marked; for example, the skin of a 70-year-old subject has approximately 25% of the 7-dehydrocholesterol compared with that of a young adult\[35\]. Cholecalciferol (and ergocalciferol) is carried in blood to the liver and hydroxylated at position 25 to form 25(OH)D. The final step in the pathway is hydroxylation of circulating 25(OH)D at the position to form biologically active 1,25(OH)₂D. This occurs in the kidney, and other tissues, and is followed by its release into blood bound to vitamin D binding protein and transported to target organs.

**How vitamin D works**
Systemic or locally produced 1,25(OH)₂D binds to the vitamin D receptor (VDR), a nuclear receptor that dimerises with the retinoid X receptor and, in turn, becomes a regulator of transcription\[36\]. Dimerisation allows interaction with the vitamin D response element on target genes initiating transcription\[37\]. The VDR is a member of the steroid receptor superfamily and is responsible for regulating transcription in many responsive genes. Indeed, more than 200 genes, including those that regulate cell differentiation and proliferation as well as multiple metabolic systems, are targets for vitamin D.

**Skin pigmentation, UVR and vitamin D**
Vitamin D photosynthesis is long-established among animals implying a key role in metabolism. Phytoplankton in the sea have synthesised vitamin D for more than 500 million years and land vertebrates for more than 350 million years. Further, the sophisticated biochemical systems used by humans to balance the harmful and beneficial effects of sunlight demonstrate the evolutionary pressures on these processes. Protection from UVR has been provided by the development of a sunscreen; eumelanin. Eumelanin absorbs UVR, reducing its penetration and, thereby, formation of potentially harmful free radicals (reactive oxygen species) in the skin. The migration of humans from Africa to environments of often low and highly seasonal UVR placed pressure on the original constitutive, dark-skinned phenotype\[38\]. Thus vitamin D₂ synthetic ability, following movement into higher latitudes, was enabled by polymorphic change in genes that determine skin pigmentation, such as melanocortin 1 receptor, with the resulting development of partially depigmented phenotypes capable of tanning. Thus, the present range of skin pigmentation results from a requirement to promote cutaneous UVR-induced vitamin D₃ synthesis (depigmented phenotype) and simultaneously prevent UVR-induced damage (pigmented phenotype)\[39\].

Studying the relationship between UVR exposure, vitamin D status, skin type and disease risk is complicated by historical and recent population movements resulting in many people living under solar regimes very different to those in which their ancestors developed mechanisms to balance sunlight’s harmful and beneficial effects. The health penalties of these movements are still under assessment though the potentially serious consequences of chronically low exposure are now being recognised. This of course, does not mitigate the need to ensure that the risks associated with inappropriate and excessive UVR exposure in terms of skin and other
cancers continues to be emphasised.

**Environmental factors affecting exposure to UVR**

The amount of UVR reaching earth varies with the angle at which radiation passes through the atmosphere (solar zenith angle), its path length through air, the presence of clouds and pollution in the lower atmosphere\[^{39,40}\]. Consequently, place and time of day and season are important. Outside of tropical latitudes, ensuring a year-round, adequate level of vitamin D synthesis is problematic because large solar zenith angles and long path lengths result in increased absorption and scattering of UVR. During the year the availability of vitamin D\textsubscript{3}-inducing UVB wavelengths varies with latitude and outside the tropics there is little or no UVB in sunlight except at high altitudes for much of the year. For example, the equator sees only about a 20% variation while 50° N (circle of latitude that crosses the English Channel, Belgium, Czech Republic, Russia, Mongolia and Canada) sees around 250% variation. Indeed, between November-February, people living at latitude 50° N and higher receive no effective vitamin D\textsubscript{3}-inducing UVB and can effect no vitamin synthesis\[^{39,40}\]. This latitude effect is compounded by dark skin pigmentation; the higher the eumelanin content the lower the vitamin D\textsubscript{3} production. Thus, for many individuals there is insufficient UVB over the year to allow adequate vitamin D synthesis and therefore a need to consume vitamin D\textsubscript{3}-rich foods such as oily fish. An additional problem in ensuring adequate vitamin D status, particularly away from the equator, is presented by modern urban lifestyles. Exposure to UVR is limited by clothing, shade-seeking behaviour, often because of skin cancer fears, and occupations that result in 80%-90% of work time being spent indoors.

**Assessing vitamin D status and defining hypovitaminosis**

Exposure to sunlight or dietary intake of vitamin D increases the serum concentration of 25(OH)D making this a ready indicator of body vitamin D status. Establishing a link between chronic hypovitaminosis and disease risk clearly requires definition of a normal serum concentration of 25(OH)D. The serum 25(OH)D concentrations that identify hypovitaminosis D are not fully defined though the following ranges have been suggested; deficiency: \( \leq 12\text{ ng/mL (30 nmol/L)} \), insufficiency: 12-20 ng/mL and satisfactory status: \( \geq 20\text{ ng/mL (50 nmol/L)} \). However, given the well-recognised seasonal variation in vitamin synthesis, particularly in northerly latitudes, any reference range needs to be considered in the context of season. Recently Tandeter described an Individual Mean Annual vitamin D level termed the "IMAD level" and a recovery formula "RF" that may be used to calculate a mean that encompasses values from four seasons\[^{41}\].

**Relationship between season and vitamin D status**

Understanding the temporal relationship between seasons, solar radiation and vitamin D photosynthesis is important if epidemiological approaches are used to establish associations between these variables, disease risk and outcome. Furthermore, the impact of relative acute or chronic hypovitaminosis on the relationship between seasons and disease pathogenesis is unclear. For example, if chronic hypovitaminosis D was pathological, a visible consequence might take some time to be clinically evident and therefore not easily associated with the seasons\[^{42}\].

Surprisingly given the potential impact of vitamin D on public health, there is little data on the relationship between seasons, serum vitamin concentrations and lag time between firstly, solar radiation and building up of adequate levels of the vitamin and secondly, which chronic patterns of hypovitaminosis have most impact on the pathogenesis of particular diseases\[^{42}\]. Thus, while the causal link between skin exposure to solar UVR and serum vitamin D cyclicity is recognised, neither the mathematical relationship between the peaks and troughs of serum 25(OH)D concentrations during the year nor how (or if) particular patterns affect disease risk have been well defined. Kasahara et al\[^{43}\] also provide a model describing the seasonality of serum 25(OH)D concentrations in the United States that could be extrapolated to other studies\[^{41}\]. They argued that in the temperate northern hemisphere, serum 25(OH)D concentrations vary during the year because production is determined by the area of skin exposed to UVR and the intensity of the radiation. Thus, serum vitamin concentrations demonstrate maximum levels in late summer and lowest in late winter. This presumably reflects significant photosynthesis and gradual accumulation of vitamin D during the early spring months and a gradual use of reserves in months immediately after photosynthesis ceases when there is little sunlight. Thus, serum vitamin D concentrations demonstrate a seasonal lag pattern that is influenced by how much atmospheric sunlight must pass through before reaching the human body.

**ASSOCIATION BETWEEN HYPOVITAMINOSIS D, THE METABOLIC SYNDROME AND CVD RISK**

**Importance of vitamin D: Population studies using mortality/morbidity as outcome**

Many studies suggest that low serum vitamin D concentrations, even when above those associated with rickets, are deleterious. A variety of criteria have been used as clinical endpoints. For example, Schöttker et al\[^{43}\] studied the association between serum 25(OH)D concentrations and mortality in a meta-analysis of data from eight prospective cohort studies involving 26018 men and women aged 50–79 years from Europe and the United States. The outcome measures were all-cause, cardiovascular, and cancer mortality. As expected, 25(OH)D concentrations were higher in summer and in
men. During follow-up a total of 6695 study participants died; 2624 of these subjects died of CVs and 2227 of cancer. Despite levels of 25(OH)D strongly varying with country, gender and season, the association between 25(OH)D concentration and all-cause and cause-specific mortality was consistent. The lowest 25(OH)D quintile was associated with increased all-cause mortality, cardiovascular mortality and cancer mortality (in those with a history of cancer). The inverse association across quintiles was consistent across countries, genders, season and age groups despite 25(OH)D cut-off values varying according to these characteristics.

Associations between UVR exposure and disease risk and outcome have been reported for a wide range of pathologies, although in most cases conflicting data have also presented. Corresponding studies using serum 25(OH)D also show conflicting data. For example, we have presented data indicating that UVR may influence disease risk by a vitamin D mediated mechanism in the pathogenesis of prostate cancer and multiple sclerosis, though we emphasise that these associations remain unproven and any mechanistic basis is uncertain.

Metabolic syndrome and seasons
Clearly, any suggestion that risk of the metabolic syndrome is partly determined by vitamin D status would be helped by evidence that the incidence of the syndrome, and/or its component phenotypes, is linked with availability of the vitamin and/or the seasons. Some evidence supporting this view is available. Kamezaki et al. reported such links in 1202 Japanese males (44 ± 10 years) who were assessed in summer and winter in 2008 for the metabolic syndrome defined using the criteria proposed by the NCEP, the IDF and the Japanese Society of Internal Medicine (JSIM). The prevalence rates of NCEP, IDF, and JSIM defined metabolic syndrome in winter were 3.8%, 15.1% and 12.4% and in summer, 3.2%, 10.7% and 8.4% respectively. Blood pressure changes were most significantly correlated with this seasonal variation in metabolic syndrome prevalence.

However, inconsistent results regarding the putative association of key components of the metabolic syndrome with season have been reported including more insulin resistance and higher triglyceride concentrations during the summer in some, winter in others and some showing no significant seasonal variation. Taiwanese subjects described by Chen et al. were studied in winter (January and February) and summer (July and August) in 2002. They found higher levels of fasting insulin, HOMA-insulin resistance and triglycerides, but lower levels of HDL-C in summer compared with winter. The prevalence of metabolic syndrome in summer was higher than in winter; difference of 7.7% in both genders (P = 0.0092 in men, P = 0.0037 in women). After controlling for BMI and other risk profiles, summer was independently and positively associated with fasting insulin and insulin resistance regardless of metabolic syndrome.

A further interesting association between the metabolic syndrome and season is the report by Rintamäki et al. showing a significant association between seasonal changes in mood and behaviour and the metabolic syndrome. Individuals with the syndrome had greater seasonal changes in mood and behaviour.

Metabolic syndrome and vitamin D status: Observational studies
Considerable research has focussed on associations between vitamin D levels and the prevalence of the metabolic syndrome and its component features. Many studies demonstrate an inverse relationship between serum 25(OH)D and diabetes, metabolic syndrome, insulin resistance and beta cell function. The NHANES data confirmed the inverse relationship between 25(OH)D levels and diabetes and insulin resistance in the non-Hispanic white and Mexican American, but not in the non-Hispanic black populations.

A meta-analysis of 28 studies (between 1990 and 2009) including 99745 participants (age range: 40.5-74.5 years) by Parker et al. investigated the effects of vitamin D on the risk of CVD, diabetes and the metabolic syndrome. Higher levels of vitamin D were seen to be associated with reduction of all the outcomes studied among middle aged and elderly individuals. The 28 studies reported 33 ORs when considering the association between 25(OH)D and cardiometabolic outcomes; 29 of these ORs suggested an inverse relationship with 3 indicating an opposite effect with 1 analysis remaining non-significant. The pooled OR was 0.57 (95%CI: 0.48-0.57). Prevalence of the metabolic syndrome was the outcome in 8 of the studies; all these showing a significant association between high 25(OH)D levels and reduced metabolic syndrome prevalence (OR = 0.49, 95%CI: 0.38-0.64).

Ju et al. studied the relationship between serum 25(OH)D levels and metabolic syndrome in the general adult population using a dose-response meta-analysis based on studies reporting risk ratios for metabolic syndrome in categories of serum 25(OH)D concentrations. The pooled OR for the metabolic syndrome per 25 nmol/L (10 ng/mL) increment in the 25(OH)D concentration was 0.87 (95%CI: 0.83-0.92), based on 16 cross-sectional studies and 1.00 (95%CI: 0.98-1.02) for 2 cohort and nested case-control studies. The dose-response meta-analysis showed a generally linear, inverse relationship between 25(OH)D levels and the metabolic syndrome in the cross-sectional studies [probability (P) value for linear trend < 0.001]. They concluded that vitamin D status was associated with metabolic syndrome risk in cross-sectional but not longitudinal studies.

Song et al. reported a cross-sectional study comprising 778 Korean adults. Metabolic syndrome was defined according to the American Heart Association/National Heart, Lung, and Blood Institute criteria and the Korean Society for the Study of Obesity. The overall prevalence of the metabolic syndrome was 18.9%. After multiple adjustments, compared with the highest
quartile serum 25(OH)D level group (19.9-55.9 ng/mL), the OR for metabolic syndrome in the lowest level group (4.2-9.7 ng/mL) was 2.44 (95%CI:1.32-4.48). The intermediate quartiles (9.8-14.1 ng/mL) and (14.3-19.8 ng/mL) had ORs of 2.20 (95%CI: 1.24-3.90) and 1.81 (95%CI: 1.02-3.20) respectively when compared to the highest quartile. Among the components of metabolic syndrome, the adjusted ORs for elevated blood pressure and high triglycerides in the lowest 25(OH)D level were 1.81 (95%CI: 1.15-2.85) and 2.74 (95%CI: 1.64-4.57) respectively. Thus, it is clear from these observational surveys that a relationship may exist between 25(OH)D levels and glucose homeostasis, metabolic syndrome and type 2 diabetes. These population studies do not hint as causation as 25(OH)D status and other established risk factors were not measured at or prior to diagnosis. Thus, prospective studies are required that take into account other confounding factors such as serial weight measurements, physical activity and family history.

**Metabolic syndrome and vitamin D status: Prospective studies**

A number of prospective studies have also presented data that support the proposal that low serum 25(OH)D concentrations are associated with increased risk of the development of the metabolic syndrome. For example, Gagnon et al. studied 4164 adults (mean age 50 years; 58% women; 92% Europids). Over the following 5 years, 528 incident cases (12.7%) of the metabolic syndrome were identified. Compared with the reference category [highest quintile 25(OH)D ≥ 34 ng/mL], the metabolic syndrome risk was significantly higher in people with 25(OH)D in the first (< 18 ng/mL) and second (18-23 ng/mL) quartiles [OR = 1.41 (95%CI: 1.02-1.95) and 1.74 (95%CI: 1.28-2.37) respectively]. Serum 25(OH)D was inversely associated with waist circumference (P < 0.001), triglycerides (P < 0.01), fasting glucose (P < 0.01), and HOMA-IR (P < 0.001) but not with 2-h plasma glucose (P = 0.29), HDL-C (P = 0.70), or blood pressure (P = 0.46).

More recently Kayaniyil et al. examined the prospective association of 25(OH)D with the metabolic syndrome in a multi-ethnic cohort of non-diabetic adults with pre-existing risk factors in Ontario, Canada. Of 654 participants enrolled at baseline, 489 attended a 3 year follow-up visit. Multivariate logistic regression analyses indicated a decreased risk of the metabolic syndrome at follow-up per standard deviation increase in baseline 25(OH)D after adjustment for sociodemographics, season, baseline and change in supplement use, physical activity and insulin resistance (OR = 0.63, 95%CI: 0.44-0.90). These conflicting findings make it essential that both interventions (weight reduction and vitamin D replacement) are studied in detail with suitably designed trials. Other studies investigating mechanisms, unlike Vimaaleswaran et al., have indicated a bi-directional association between obesity and hypovitaminosis D. It has been seen from animal studies that vitamin D may play a part in adipogenesis and energy metabolism. The VDR is expressed in adipose tissue pre-maturation and in early adipogenesis. The presence of a role in adipogenesis is also suggested by adipocyte atrophy seen in VDR knockout mice. The relationship between volume of adipose tissue and vitamin D status, at least as reflected in serum 25(OH)D concentrations, is unclear. Vitamin D is sequestered in adipose tissue and it has been speculated that obesity, by increasing the volume of distribution of available adiposity, will lead to lower serum vitamin D levels. This view is contradicted by Pramyothin et al. who measured vitamin D levels in the subcutaneous
abdominal fat of 17 patients undergoing gastric bypass. Vitamin measurements were made at surgery and over a 12 mo follow-up period\textsuperscript{[69]}. It was found that vitamin D levels in adipose tissue varied considerably and no significant change in serum 25(OH)D was noted during follow-up despite intake of supplements (> 2500 U/d).

There has been speculation that behaviour traits associated with obesity, such as reduced outdoor exercise levels, could be associated with decreased exposure and reduced vitamin D synthesis. Results from studies investigating this possible association have varied\textsuperscript{[76,71]}. Thus, although a clear association is evident between adiposity and vitamin D levels the nature of this association has yet to be determined. It is important to establish this relationship as central adiposity is a key driver in the development of the metabolic syndrome.

Dysfunction of insulin secretion by pancreatic beta cells and insulin resistance are considered to be causative drivers in the aetiology of type 2 diabetes\textsuperscript{[26]}. Insulin secretion may be affected by lipotoxicity, due to increased free fatty acids, and glucotoxicity, due to elevated serum glucose and lipid accumulation within the beta cells\textsuperscript{[72]}. We have seen that insulin resistance is a core component of the metabolic syndrome. Contrasting findings are evident in observational studies investigating the relationship between 25(OH)D levels and insulin sensitivity. Chiu et al\textsuperscript{[32]} in Californian students of mixed ethnicity, and Kamycheva et al\textsuperscript{[23]}, in a study of patients with hyperparathyroidism, [patients grouped by the median 25(OH)D concentration] noted a positive correlation between insulin sensitivity and 25(OH)D levels. However, there have been other studies which have not shown the above association, these having been carried out in patient groups characterised by obesity\textsuperscript{[79]}, non-diabetic status\textsuperscript{[73]} and the metabolic syndrome\textsuperscript{[80]}. A prospective study of 524 non-diabetic individuals by Forouhi et al\textsuperscript{[77]} showed an inverse association between 25(OH)D levels and the risk of insulin resistance and elevated blood sugars\textsuperscript{[77]}. However, the Mini-Finland Health Survey did not demonstrate a significant correlation between 25(OH)D quartiles and the onset of diabetes when the analysis was corrected for BMI and activity\textsuperscript{[78]}.

Vitamin D supplementation has been seen to alter insulin sensitivity in non-diabetic patients, but not in patients diagnosed with type 2 diabetes\textsuperscript{[79,80]}. Pittas et al\textsuperscript{[81]} demonstrated that, when compared to placebo, vitamin D had a positive effect on insulin resistance and glycaemic control (non-primary outcome) in a randomised controlled study of patients with impaired fasting glucose\textsuperscript{[81]}. A complex mechanism is suggested by the SURAYA trial of obese south Asian women as insulin resistance was seen to improve only when supplementation elevated the 25(OH)D concentration above 80 nmol/L this perhaps indicates either a dose response or threshold effect\textsuperscript{[82]}.

Given the association between 25(OH)D levels and obesity it is expected that there would be a similar relationship with the lipid concentrations; however, study results have varied. A large study in Norway, both longitudinal \textit{(n = 2159)} and cross sectional \textit{(n = 10105)} demonstrated that higher levels of cholesterol, HDL-C and LDL-C and lower levels of triglyceride were associated with reduced 25(OH)D concentrations\textsuperscript{[83]}. A survey of 108711 patients who had multiple 25(OH)D and lipid profiles measured revealed a similar relationship between 25(OH)D and cholesterol and LDL-C levels\textsuperscript{[84]}. Further, optimal levels of 25(OH)D were associated with higher HDL-C\textsuperscript{[84]}. More confusion has arisen as vitamin D supplementation following their cross sectional survey in patients with hypovitaminosis did not lead to consistent changes in the lipid profile\textsuperscript{[84]}. Jorde et al\textsuperscript{[85]} reviewed the findings of 22 cross sectional and 10 placebo controlled double blind randomised controlled trials and concluded that, while the cross sectional studies demonstrated a uniform inverse relationship between 25(OH)D and triglyceride levels, the intervention studies with vitamin D supplementation have led to varied results. They concluded that these intervention studies were not adequately designed to specifically investigate the relationship between 25(OH)D and lipids and speculated that the relationship between 25(OH)D and lipids could be either direct or via changes in parathyroid hormone and/or calcium concentrations\textsuperscript{[85]}.

Many studies using mouse and human hepatoma cell lines\textsuperscript{[86,87]} and VDR knockout mice\textsuperscript{[88]} have been carried out to understand the observed associations between 25(OH)D and lipid concentrations. Some have examined the effect of VDR on bile acid synthesis, and cholesterol levels, once again with inconsistent results\textsuperscript{[89]}.

Hypertension, one of the defining components of the metabolic syndrome, has been reported to display a seasonal and geographical variability raising the possibility of sun exposure having a role\textsuperscript{[90]}. Even before this observation Resnick et al\textsuperscript{[91]} in 1986 suggested that vitamin D metabolites were associated with hypertension potentially via the renin-angiotensin system\textsuperscript{[91]}. Both animal and cross-sectional human studies have suggested vitamin D to be an inhibitor of the renin-angiotensin system in VDR knockout\textsuperscript{[92]} and 1α-hydroxylase knockout\textsuperscript{[93]} mice with significantly raised renin activity and plasma angiotensin 2 concentrations. The effects were reversed in the 1α-hydroxylase knockout mice by administration of 1,25(OH)\textsubscript{2}D\textsuperscript{[93]}. Vascular smooth muscle and endothelial cells express VDR and the 1α-hydroxylase enzyme indicating that vitamin D may influence endothelial function which could lead to arterial stiffness and hypertension, in addition to plaque formation\textsuperscript{[94]}. The change in endothelial function could be due to either a direct effect or via improved blood pressure.

Most of the surveys such as NHANES III\textsuperscript{[95]}, the German National Health Interview and Examination Survey\textsuperscript{[96]} and the 1958 British Birth Cohort\textsuperscript{[97]} investigating the relationship between vitamin D and hypertension have pointed to an inverse association. However, there have been studies that have not shown this...
association \cite{98, 99}. Once again the mixed findings could have been due to confounding variables common in multifactorial pathology. Similarly prospective studies too have not been consistent with regards to outcome \cite{100, 101}. Further, interventional trials have also resulted in varied results \cite{102, 103}. A meta-analysis of 11 interventional trials showed a modest reduction in diastolic blood pressure (3.1 mmHg), but this was not accompanied by any significant change in systolic blood pressure \cite{104}. It was evident that most of the studies were not designed to investigate the association in question. Although observational studies have suggested endothelial dysfunction in individuals with hypovitaminosis D \cite{105, 106} results following vitamin D supplements have been missed. While some intervention trials have shown a beneficial effect on endothelial function \cite{107, 108} others have not \cite{109, 110}. Thus, it is clear that although most studies indicate an association between vitamin D status and blood pressure the findings from observational, prospective and interventional studies have not been unanimous.

We have seen that much of the work presented above, with the exception of Karatas et al \cite{59}, has focussed on individual associations between hypovitaminosis D, vitamin D supplementation and components of the metabolic syndrome. As evident from Figure 1 these factors are inter-related and it is essential that future studies take this into account.

**Benefits in mortality, CVD and onset of type 2 diabetes observed following vitamin D supplements**

As we have seen previously there is considerable evidence that hypovitaminosis D is associated with increased CVD risk although the mechanisms still remain largely unclear. It is essential to determine if this increase in risk can be reversed by supplements. Many questions remain that can only be answered by long term intervention studies. It is important to estimate benefit in the overall study group as well as subgroups based on age, gender, ethnicity, CVD risk, vitamin D levels and other baseline characteristics. Further, benefit associated with different replacement dosage must be evaluated. To date no large intervention trial fulfilling the above criteria has reported findings.

Vacek et al \cite{111} in 2012 carried out an observational retrospective study of 10889 patients seen in a secondary care cardiology setting. Hypovitaminosis (< 30 ng/mL) was diagnosed in 70.3% of this cohort. Vitamin D supplements were taken by 31.6% of the population. No changes were observed in any of the outcome measures. It must be noted that this study was in a selected population and was retrospective and observational. Gotsman studied the impact of vitamin D supplements on mortality in 3069 patients with heart failure \cite{112}. Supplementation was associated with significantly reduced mortality (HR = 0.68, 95%CI: 0.54-0.85). However, no convincing data exists regarding the benefits in mortality that may be related to vitamin D supplements in a healthy population.

There are very few studies examining CVD risk reduction following vitamin D supplementation. A systematic review of 17 prospective and randomised trials using vitamin D and/or calcium supplements showed vitamin D supplements, at approximately 1000 IU/d, caused a 10% relative risk reduction that was not significant when compared to placebo \cite{113}. When the analysis was restricted to the 5 prospective studies of patients receiving vitamin D a reduction in CVD related mortality was observed. It must be noted that 4 of these studies consisted of patients receiving dialysis, a high risk group. Interestingly calcium supplementation did not appear to influence any of the outcome measures.

No large randomised control trial has been carried out with onset of metabolic syndrome/diabetes as the primary outcome. The RECORD study where patients were randomised to receive 800 IU/d of vitamin D recorded onset of type 2 diabetes as a secondary outcome (primary outcome was fracture rate) \cite{114}. A nonsignificant 33% relative risk reduction was seen. Similarly, onset of diabetes was the monitored outcome in the Womens Health Initiative Calcium/Vitamin D Trial with 33951 women randomised to either 400 IU/d of vitamin D or placebo for 7 years and no significant benefit was observed \cite{115}. Most other studies have included smaller patient numbers and have not demonstrated reduced incidence of type 2 diabetes or the metabolic syndrome. Further, no convincing evidence exists that supplementation reduces the progression from the metabolic syndrome to type 2 diabetes.

Mixed results have been observed when insulin sensitivity has been determined following treatment with vitamin D. Mitri et al \cite{116} demonstrated a significant improvement in insulin secretion in 92 individuals at high risk of developing diabetes following randomisation to either 2000 IU/d of vitamin D supplements or placebo. Nagpal et al \cite{117} determined the effect vitamin D supplementation (3 doses of 120000 IU) had on insulin sensitivity compared to placebo in 71 healthy male volunteers with central obesity. Insulin sensitivity was seen to improve in the treatment arm \cite{117}. However, there have been other trials demonstrating no improvement in insulin sensitivity. Luo et al \cite{118} treated 21 Chinese patients with type 2 diabetes and hypovitaminosis D (≤ 50 nmol/L) with 2000 IU/d of vitamin D for a 3 mo period. No changes were observed in any of the metabolic syndrome parameters, HbA1c or in insulin requirements \cite{118}. George et al \cite{119} published a systematic review of 15 trials assessing the effects of vitamin D supplementation compared to placebo on fasting glucose,
glycaemic control and insulin resistance. When all the studies were combined no significant improvement in outcomes was observed. When the analyses were restricted, to patients with diabetes or impaired glucose tolerance, significant but small improvements were observed in both fasting glucose and insulin sensitivity, but no changes seen in HbA1c\(^{119}\).

All the studies described above leave an impression that vitamin D supplementation could potentially be beneficial. However, current evidence does not allow us to identify patient groups that would benefit maximally.

**Vitamin D and type 2 diabetes**

We have focussed this review on hypovitaminosis D in the metabolic syndrome and its defining components as well as CVD. We have described that hypovitaminosis D appears to be related to the metabolic syndrome, potentially a pre-diabetic state and its component characteristics such as obesity and insulin resistance. Thus, we would expect there to be a relationship between vitamin D levels and type 2 diabetes. We have also described current evidence as to the effects of vitamin D supplementation on diabetes control. In addition to actions that may be mediated via obesity and insulin resistance which we have described above, hypovitaminosis D appears to have a direct effect on glycaemic control. It has been suggested that vitamin D could have a role in ensuring calcium influx into cells which may be essential to the actions of insulin in skeletal muscle and adipocytes\(^{120}\). There have been hints that elevated parathyroid hormone levels may blunt the actions of insulin\(^{121}\). Although outside the boundaries of this review, an association between type 1 diabetes and hypovitaminosis D also suggests at a direct action of vitamin D on insulin action that may also be relevant to type 2 diabetes\(^{122}\).

**Vitamin D and non-alcoholic fatty liver disease**

Individuals with the metabolic syndrome of long duration are considered to be at greater risk of developing hepatic steatosis\(^{123}\). A two or three hit hypothesis has been proposed\(^{124}\). The first hit is considered to be the damage caused by fatty infiltration associated with insulin resistance and obesity\(^{124}\). The second and third hits are thought to be due to hepatic injury resulting from mechanisms linked to oxidative stress and impaired cellular regeneration\(^{124}\). Hepatic fatty infiltration could progress through non-alcoholic steatohepatitis and liver fibrosis to liver cirrhosis. Management of this spectrum has focused on improving the metabolic syndrome phenotype with weight reduction and management of dyslipidaemia and hyperglycaemia\(^{125}\).

As hypovitaminosis D is related to the metabolic syndrome we would expect an association with non-alcoholic fatty liver disease. A review of 6800 patients on the NHANES III database showed that those with an elevated serum alanine transaminase activity were seen to have lower vitamin D concentrations compared to matched controls with normal enzyme levels, the analysis being corrected for the metabolic syndrome\(^{126}\). This association (independent of age, gender, triglycerides and insulin resistance) was also observed by Barchetta et al\(^{127}\) in a study of 262 patients. Further, vitamin D levels were lower in patients with non-alcoholic fatty liver disease diagnosed by liver biopsy\(^{128}\). Hypovitaminosis D has been associated with altered regulation of inflammatory and anti-oxidant pathways in addition to influencing the metabolic syndrome phenotype; all the hits postulated in the aetiology of steatosis\(^{129}\). At present there is no conclusive evidence that vitamin D supplementation could lead to clinical improvement of hepatic steatosis. Interestingly treatment with agents such as ursodeoxycholic acid, which increases vitamin D concentrations, has shown some improvement in non-alcoholic steatohepatitis with alanine transaminase levels used as the outcome\(^{130}\). However, ursodeoxycholic acid may possess direct anti-inflammatory anti-oxidant properties which may be significant confounding factors.

**CONCLUSION**

It is clear that hypovitaminosis D has extra-skeletal effects that impact on the development of various pathologies including those that make up a large majority of morbidity and mortality; cancer, CVD and diabetes. In this review we have focussed on the association between hypovitaminosis D and the metabolic syndrome. Recently there has been a significant increase in the number of individuals with the metabolic syndrome. Indeed, as much as 40% of the United States population suffers from the condition comprising some or all of a cluster of CVD risk factors. Although the metabolic syndrome does not confer additional risk compared to the component risk factors we believe it helpful to the clinician and researcher to classify patients because it encourages a holistic approach to CVD risk reduction and study of the inter-relationships between the different relevant factors respectively.

There is considerable confusion surrounding the association between vitamin D and the metabolic syndrome, its component factors, CVD and mortality. Although studies have not been unanimous in their findings we are left with the impression that hypovitaminosis D is probably associated with all the above outcomes. However, the nature of this relationship in subgroups (e.g., gender, age groups, ethnicity, etc.) is not clear. The risk associated with varying levels of vitamin D has not been estimated. Mechanisms that lead to increased prevalence of the components of the metabolic syndrome and its associated risk have not been worked out. Even more confusing is whether there is any benefit in vitamin D replacement therapy as trials have been contradictory.

However, there appears to be sufficient evidence to make the unravelling of the association between hypovitaminosis D and the metabolic syndrome a priority. Today both conditions are of high prevalence. This suggests that even if a modest decrease in CVD risk is
observed following vitamin D replacement it will translate to substantial overall benefits. Due to the modest price of supplements and relative safety, the cost benefits could be in favour of vitamin D replacement.

What is required are well designed studies, both prospective and intervention. In addition to estimating overall benefit, they must be sufficiently powered to study subgroups as well as risk and benefits at varying serum vitamin D concentrations as well as replacement regimes. It is only following the availability of this data that clear recommendations can be made with regards vitamin D replacement in patients with the components of the metabolic syndrome.

REFERENCES


16 Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care 2003; 26: 2745-2749 [PMID: 16249550]


25 Reilly MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? Circulation 2003; 108: 1546-1551 [PMID: 14517150 DOI: 10.1161/01.CIR.0000088846.10655.E0]


Pietre D, 2013; Heger A, Berlanga AJ, Maugeri NJ, Lincoln, Park CH. Low serum vitamin D level is associated
2014; 2004; 2012; Challenging the present definition of “normal”, Chaplin G. Human skin pigmentation, migration
2004; Fryer AA, Strange RC. Ultraviolet radiation, vitamin D: new insights 2004; Luscombe CJ, Strange RC. Vitamin D: new insights
2011; Chu A, Go VL, Saad MF. Hypovitaminosis D is
2007; Boucher BJ, Feskens EJ, Kromhout D. Vitamin D, Seasonality in the United States.
2007; 2012; Hekimsoy Z, Dinc G, Onur E, Ozmen B. Vitamin
39 45 41 38 37 34 33 35 32
Strange RC et al. Vitamin D and the metabolic syndrome


Strintzi K, Lykourgiotis M, Kapsogeorgou E, Kaskenas D, Kalamaki E, Dalakas MC. Normal 25-hydroxyvitamin D levels are associated with reduced skeletal muscle mass and increased mortality in patients with type 2 diabetes mellitus. Diabetes Care 2008;31:782-87

Strong RC, Austin DP, Khan AM. The role of vitamin D in the metabolic syndrome. Diabetes Care 2010;33:923-925


Vitamin D supplementation in early childhood and risk for Type 1 (insulin-dependent) diabetes mellitus. The EURODIAB Substudy.


129 **Kwok RM**, Torres DM, Harrison SA. Vitamin D and nonalcoholic fatty liver disease (NAFLD): is it more than just an association? *Hepatology* 2013; **58**: 1166-1174 [PMID: 23504808 DOI: 10.1002/hep.26390]


P- Reviewer: Kluge M  S- Editor: Tian YL  L- Editor: A  E- Editor: Liu SQ