Editorial

Vitamin D research and public health nutrition: a current perspective

This 2017 special issue of Public Health Nutrition features nineteen research manuscripts all relevant to the role of vitamin D nutritional status in the risk and prevention of chronic diseases of public health importance. A useful barometer gauging the worldwide growing interest in vitamin D and health research is shown by over 13,000 studies abstracted in PubMed over the last 5 years alone, all with a focus on vitamin D. Vitamin D deficiency in Europe is associated with adverse health outcomes whose direct and indirect medical cost burdens have been estimated in the hundreds of billions of Euros, which underlines the importance of this work to public health(1). Dedicating a special issue to these recently accepted vitamin D studies provides Public Health Nutrition editors with an opportunity to set in perspective the diverse aspects of the continuing growing interest in vitamin D nutritional status, its health importance, and the impact of the many recent innovations in analytical methods, assay standardization programmes and the underlying factors contributing to the controversy over serum cut-off values defining vitamin D nutritional status. Newer standardized analytical methods now enable research exploring the many gaps in our understanding of vitamin D nutritional status which many of these papers address, as well as the association with reduced risk of disease and other beneficial health effects.

The common feature among all the papers in this special issue is the measurement of vitamin D status or the circulating concentrations of 25-hydroxyvitamin D (25(OH)D, nmol/l or ng/ml). There is a growing demand to assess vitamin D status in order to screen for deficiency, monitor efficacy of supplementation or fortification, or assess the association between vitamin D status and chronic diseases including osteoporosis, diabetes, cancer, CVD, infection and autoimmune or neurological disorders. To meet this demand, less labour-intensive assay methods have been developed along with certified external standards and proposed criteria for defining vitamin D deficiency/sufficiency(2–5).

The goal of this perspective is to inform researchers about the currently accepted assay methods and quality control procedures used to determine 25(OH)D concentrations and the most widely accepted criteria for establishing vitamin D status. We present some background information describing relevant new evidence in four areas defining important public health gaps in knowledge that are addressed by many of the studies in this issue. Our intent is to provide insight into how these studies contribute to these gaps in our understanding of vitamin D status and, more importantly, how the study findings may impact public health nutrition policy and practices.

Gaps in vitamin D understanding relevant to public health

The four areas addressing critical gaps in our knowledge of vitamin D status and health that were tackled by the studies in this special issue include: (i) global vitamin D deficiency and association with health risk; (ii) impact of or need for national vitamin D food fortification; (iii) vitamin D supplement use in vulnerable populations; and (iv) season and sunlight influence year-round. Among these areas, global vitamin D deficiency and association with health risk was the most repeated manuscript focus and is clearly the most controversial. Recent evidence supports global vitamin D deficiency(6,7) and numerous systematic reviews and meta-analyses examining multiple health outcomes and mortality risk(8–11) show association with vitamin D deficiency, notably when individual participant data are used in the meta-analyses(11). However, these findings are largely based on data from European and higher-income countries, underscoring the need for and importance of diverse geographic studies such as the ones presented in this issue.

Evidence of global vitamin D deficiency and its association with adverse health speaks to the need for national food fortification programmes, both in Europe and lower- and middle-income countries(12,13). Fortification of food is the most effective population-based approach to correcting poor vitamin D status(13), while supplementation of specific groups at high risk within a population is a targeted intervention to rapidly correct serious deficiencies. Even in countries with year-round abundant sunshine for endogenous skin synthesis of vitamin D, recent findings show there is a need for national food fortification programmes in order to reach the entire population, again stressing the necessity for worldwide studies(14). Vitamin D supplement use faces many barriers as a population strategy to prevent vitamin D deficiency and adverse health outcomes(15), although supplementation may prove effective in small groups or individuals at risk(16,17). Nevertheless, caution is warranted for individuals who self-medicate out of necessity in countries where sun is avoided, food is not fortified and vitamin D supplements are not well regulated, such as India(10). More geographically diverse studies are needed exploring the efficacy of vitamin D supplement use in vulnerable populations, especially during

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pregnancy and early infancy. Vitamin D supplement use has been shown to be effective in populations where sun exposure is limited during the winter\(^\text{17,18}\). Seasonal changes and sunlight availability alone are unable to explain seasonal differences in countries’ population vitamin D status when their populations experience the same limited sunlight. This finding points to the need to assess other contributing sources such as diet and other confounding lifestyle factors when developing strategies to prevent vitamin D deficiency\(^\text{19}\).

Knowledge of the effective sunlight (UVB) availability during each season has recently been used to develop an integrated predictive model of serum 25(OH)D concentrations that can be applied to fortification and supplementation strategies to prevent seasonal vitamin D deficiency\(^\text{20}\). Such models were used to show similar UVB availability in northern European countries, each of which showed similar decreases with latitude and seasonal changes, but different magnitudes of seasonal fluctuations in serum 25(OH)D were observed, ostensibly due to differences in the vitamin D content of the diet\(^\text{19}\). Yet again, these findings are based on European data, leaving a gaping hole in our understanding of the interaction between season, environment, cultural lifestyle, dietary sources and vitamin D status in other countries.

**Need for global consensus on the definitions of vitamin D nutritional status**

To better understand the global importance of vitamin D deficiency to public health, a consensus must be reached on the definition of what serum concentration of 25(OH)D to use to define a deficient state. Concentrations ranging from 25 to 75 nmol/l (<10 to <30 ng/ml) have been proposed as cut-off measures for deficiency using standardized assays not sufficient to provide protection against rickets and osteomalacia (adverse bone events; <30 nmol/l or <12 ng/ml); while sufficiency represents concentrations not at risk for adverse bone events (>50 nmol/l or >20 ng/ml)\(^\text{22}\). The Institute of Medicine report did not define optimal vitamin D status; nevertheless, other scientific experts define serum concentrations exceeding 75 nmol/l (30 ng/ml) as optimal, especially for those individuals at greater risk due to disease, race or other factors\(^\text{22,23}\). There is growing but inconsistent evidence of associations between chronic disease conditions other than skeletal with serum concentrations below this range\(^\text{24}\). More convincing evidence is warranted with respect to cancer risks for which lower risks have recently been reported with higher serum concentrations of 25(OH)D\(^\text{20}\); while concentrations below 75 nmol/l (30 ng/ml) determined with standardized assays have been associated with increased risk of all-cause mortality\(^\text{21}\). Serum concentrations between 125 and 150 nmol/l (50 and 60 ng/ml) are defined as being safe and were used to define the Tolerable Upper Intake Level (UL), based on the belief that the risk for adverse health effects rises with vitamin D intakes above the UL\(^\text{22,25}\). Vitamin D toxicity is defined as serum concentrations above 250 nmol/l (100 ng/ml) and the physiological state of vitamin D toxicity is characterized by a number of serious adverse health conditions including severe hypercalcaemia\(^\text{26}\).

The key to developing appropriate dietary guidelines for the prevention of vitamin D deficiency lies in the standardization of the assays used to measure 25(OH)D and the evaluation of the assay results against cut-off values for serum concentrations that correspond to well-defined vitamin D-deficient states or conditions, which may not always be specific for bone. The importance of standardizing 25(OH)D assays cannot be emphasized enough to future investigators exploring the optimal concentrations associated with reduced risk of chronic and infectious disease\(^\text{27}\).

**Table 1** Definition of vitamin D status by 25-hydroxyvitamin D (25(OH)D) concentration relevant to healthy populations

<table>
<thead>
<tr>
<th>Serum 25(OH)D concentration</th>
<th>Status classification</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 nmol/l</td>
<td>Deficiency, at risk for rickets (infants and children), osteomalacia or osteoporosis</td>
<td>The 2011 IOM defines vitamin D deficiency as being at risk for adverse bone conditions such as rickets and osteomalacia(^\text{22}).</td>
</tr>
<tr>
<td>&gt; 12 nmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20 nmol/l</td>
<td></td>
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</tr>
<tr>
<td>75–125 nmol/l</td>
<td>Optimal or vitamin D adequate for non-skeletal effects of vitamin D</td>
<td>Evidence of protection against chronic disease conditions exists when serum concentrations are in this range. Evidence for decreased risk of cancer is observed in this range, but warrant further study(^\text{10}).</td>
</tr>
<tr>
<td>30–50 nmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125–150 nmol/l</td>
<td>Upper Level</td>
<td>Concentration set by the 2011 IOM and 2013 EFSA reports as the upper safe level(^\text{22,26}).</td>
</tr>
<tr>
<td>50–60 nmol/l</td>
<td>Potential toxicity above this concentration</td>
<td>Concentration resulting from chronic ingestion of 250 µg (10 000 IU) vitamin D, above which adverse effects may be observed(^\text{22,26}).</td>
</tr>
<tr>
<td>250 nmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 nmol/l</td>
<td></td>
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</tbody>
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IOM, Institute of Medicine; EFSA, European Food Safety Authority.
Examining gaps in knowledge important to public health nutrition policy and application

The nineteen vitamin D research papers featured in this issue explore a number of important research gaps that are vital to our understanding of the need for food fortification or supplementation programmes in less studied low- and middle-income countries and high-risk populations in higher-income countries (40–58). The majority of these studies examined aspects of global vitamin D deficiency and association with health risks (40,42,43,45–48,50–53,56–58). Two explored the impact or need for a national vitamin D food fortification programme due to seasonal challenges or deviation from traditional diets (44,54), while one explored the efficacy of vitamin D supplement use in a vulnerable population (41) and two determined the influence of season and sunlight availability year-round on vitamin D status (49,55). Several studies used nationally representative data from higher-income countries that included different race/ethnicity groups, allowing assessment of confounding anthropomorphic influences such as waist circumference, BMI, serum lipids and skin pigmentation (46,52,53).

These papers bring together valued information on vitamin D status from less studied areas of the world, including Bangladesh (43,49), China (42), Guatemala (49), India (55), Iran (40), Malaysia (50) and Mexico (56). Many used state-of-the-art standardized assay methodology, i.e. LC-MS/MS (43,47,48,54), while others used ELISA, CLIA (42,45,49,53,55–57) or HPLC (40) to analyse serum 25(OH)D concentrations, and some reported some standardization (47,48,53,56). These differences emphasize our need to standardize the assays used to clearly understand the global extent of vitamin D deficiency and insufficiency. Such understanding can only be achieved if researchers agree to use the same clearly defined measures of serum 25(OH)D concentrations to indicate vitamin D deficiency, insufficiency and sufficiency, as shown in Table 1. With assay standardization and use of the same threshold values for vitamin D status, we can gain insight into global areas in need of public health nutrition policies enabling vitamin D food fortification and supplementation.

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