Vitamin D in the Irish Population: An Analysis of Prevalence and Determinants

Helena Scully BAgSc, MSc

A thesis submitted for the degree of Doctor of Philosophy at the University of Dublin,

Trinity College

Supervisors: Dr Kevin McCarroll, Dr Eamon Laird

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Declaration

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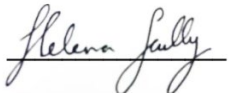

Helena Scully

I dedicate this thesis to my son Adam
for being the light, my vitamin D, in life.

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I. Summary/Abstract

Introduction:

Vitamin D has an established role in bone and muscle health, with deficiency causing rickets in children, osteomalacia in adults and contributing to the development of osteoporosis. More recently it has been associated with extra-skeletal effects including inflammation, cardiovascular disease (CVD), diabetes, cognitive impairment, and respiratory conditions including asthma and COVID. Due to a northern latitude (51-55°N), and limited dietary intake, the Irish population are at risk of vitamin D deficiency. However, much is unknown about the status in the population with regard to particular groups including children, ethnic minorities, urban dwellers, and younger adults. There is also a lack of research on vitamin D testing in Ireland including indications for same and the associated costs. Furthermore, no recent studies have assessed vitamin D intake in Irish adults, and few have examined peoples understanding of vitamin D's role in health. This PhD aims to review existing research to-date in Ireland on vitamin D, and to investigate vitamin D status and its associated determinants in an Irish population. Furthermore, it explores vitamin D retesting, with a focus on inappropriate testing and its associated costs.

Methods:

A literature review of existing evidence examining vitamin D status and intake between 1990-2022 in Ireland (Republic and Northern Ireland) was undertaken. To examine vitamin D status in the Irish population, a database of patients who had 25(OH)D serum concentration assessed by Liquid Chromatography Tandem Mass Spectrometry at St James's Hospital Dublin between 2014-2020 at the request of Primary Care physicians was generated. Statistical analysis was used to determine vitamin D status and its predictors in children (1-17 years) and adults (>18 years), including non-nationals. Vitamin D retesting and associated costs were also ascertained. Finally, a stratified sample of participants completed a questionnaire to further explore the biophysical, lifestyle and dietary determinants of vitamin D status.

Results:

From the comprehensive literature review, 142 studies and 7 reports were identified. Vitamin D deficiency (<30 nmol/L) was prevalent in Ireland, in up to 32% of older adults (>50 years), 38% of

adults (<50 years) and 68% of children (<18 years). Adolescents, younger adults, and ethnic minorities were at greatest risk. Dietary intake was lowest in children and pregnant women, and highest in older adults. Results of our first investigation based on data analysis of community dwelling adults (n=36,466) found 15% were vitamin D deficient (<30 nmol/L), increasing to 23% in winter. Younger adults (18-39 years), males and those living in low socioeconomic locations were most at risk. In my second study, one in four adults were found to have vitamin D levels retested, with inappropriate testing resulting in €60,000 of estimated wasted expenditure per annum to St James's hospital. In the third study, based on an analysis of vitamin D results of 1,226 children, 23% were vitamin D deficient, with a higher prevalence in females, older children (>12 years) and those living in poorer socioeconomic areas. Finally in my fourth study, total dietary vitamin D intake, ethnicity and sun habits were found to be important predictors of vitamin D status. Awareness of vitamin D supplementation recommendations and testing indications were poor, though knowledge of its importance for bone health were well known.

Conclusion:

Vitamin D deficiency is highly prevalent, with a lack of research in subgroups of the population at risk of deficiency including children, younger adults, pregnant women, and ethnic groups. We also identified that younger adults, adolescents, and those living in low socioeconomic areas were most at risk of deficiency. Despite vitamin D retesting being common, there was no research on its testing indications, with many adults having levels assessed for non-specific reasons and at considerable cost. The majority of adults were also not meeting a dietary vitamin D intake of 10 μg/day and had poor awareness of the current recommended dietary allowance. The findings suggest that public health measures to address deficiency in the Irish population are urgently required, such as systematic fortification of staple foods, and establishing targeted recommendation for vulnerable population groups. In addition, clear guidance for General Practitioners and the public on the appropriate indications for vitamin D testing is necessary to reduce inappropriate referrals and expenditure.

II. Lay Abstract

Vitamin D has generated a lot of recent interest. Long-term deficiency can result in the softening of the bones and cause rickets in children and osteoporosis in adults. Vitamin D may also be linked with other conditions such as cancers, heart disease, autoimmune diseases and COVID. Apart from supplements, about 80-90% of vitamin D is made by our skin in response to sunlight. However, food intake, physical and lifestyle factors also have an important influence on vitamin D status. In Ireland, we are at risk of vitamin D deficiency due to a limited source of vitamin D from food and our northern latitude (51-55°N) resulting in a lack of sunlight. As a result, our ability to make vitamin D is limited between the months of October and March, causing in a 'vitamin D winter'. Learning more about vitamin D status in the Irish population is important to gain an understanding of health and how many people may benefit if their status improves.

We aim to explore vitamin D in the Irish population to see who has low vitamin D, and what are their common factors such as age, sex, and socioeconomic status. Once we have learned how many people face this common deficiency, we will carry out a questionnaire study to collect detailed information regarding diet and other factors that influence vitamin D status. This study will provide very valuable information by helping to see what vitamin D status is in Ireland, and to help understand the factors that influence it.

III. Aims and Hypothesis of the Project

(1) To determine vitamin D status in an Irish population of children and adults in Dublin and surrounding areas.

(2) To explore in detail the factors (dietary, lifestyle, biophysical and environmental) affecting vitamin D status.

(3) To examine the factors and predictors of vitamin D testing and re-testing, with evaluation of the associated cost implications.

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List of Abbreviations

25(OH)D	25-Hydroxyvitamin D
1,25(OH)$_2$D	1,25 dihydroxyvitamin D
ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance.
BMI	Body Mass Index (Kg/m^2)
CD	Crohn's Disease
CI	Confidence Interval
CIA	Chemiluminescence Immunoassay
CIS	Clinically Isolated Syndrome
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus Disease
CUH	Children's University Hospital Study
CVD	Cardiovascular Disease
CYP27B1	1-alpha-Hydroxylase
DEQAS	Vitamin D External Quality Assessment Scheme
DOH	Department of Health
ECLIA	Electrochemiluminescence Immunoassay
EFSA	European Food Safety Authority
ELISA	Enzyme-Linked Immunosorbent Assay
ELSA	English Longitudinal Study of Ageing
EU	European Union
EVID	Evaluation of Vitamin D Study
FFQ	Food Frequency Questionnaire
FGF	Fibroblast Growth Factor
FSAI	Food Safety Authority of Ireland
GDPR	General Data Protection Regulation
GM	Geometric Mean
GP	General Practitioner
HCP	Healthcare Provider
HPLC	High-Performance Liquid Chromatography
HOMA	Homeostatic Model Assessment
HSE	Health Service Executive

IBD	Inflammatory Bowel Disease
IDEFICS	Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in Children and Infants
IOM	Institute of Medicine
IQR	Interquartile Range
ISO	International Organization for Standardization
IU	International Units
IUNA	Irish Universities Nutrition Alliance
KIGGs	German Health Interview and Examination Survey for Children and Adolescents;
LAVID	Lab Analysis of Vitamin D
µg	Microgram
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
MS	Multiple Sclerosis
NAM	National Academy of Medicine
NANS	National Adult Nutrition Survey
NDNA	National Diet and Nutrition Survey
NHANES	National Health and Nutrition Examination Survey
NI	Northern Ireland
NIH	National Institutes of Health
NIST	The National Institute of Standards and Technology
NNT	Number Needed to Test
NOAEL	No Observed Adverse Effect Level
NPSNS	National Pre-School Nutrition Survey
OH	Orthostatic Hypotension
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
PBA	Protein Binding Assay
PTH	Parathyroid Hormone
RCT	Randomised Control Trial
RDA	Recommended Dietary Allowance
nmol/L	Nanomoles Per Litre
RIA	Radioimmunoassay
ROI	Republic of Ireland
ROLO	Randomised Control Trial of Low Glycaemic Index Diet During Pregnancy

SACN	Scientific Advisory Committee on Nutrition
SD	Standard Deviation
SE	Standard Error
SES	Socioeconomic Status
SGA	Small for Gestational Age
SJH	St James's Hospital
SLE	Systemic Lupus Erythematosus
TILDA	The Irish Longitudinal Study on Ageing
TUDA	Trinity, Ulster, and Department of Agriculture Cohort Study
TUH	Tallaght University Hospital
UK	United Kingdom
UV-B	Ultraviolet-B
VAT	Value Added Tax
VDBP	Vitamin D Binding Protein
VDD	Vitamin D Deficiency
VDR	Vitamin D Receptors
VDSP	Vitamin D Standardization Program
WHO	World Health Organisation

Chapter 1: Vitamin D in Ireland: A Review of Existing Evidence

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Included in this review is reference to the published study, "A High Prevalence of Vitamin D Deficiency Observed in an Irish South-East Asian Population: A Cross-Sectional Observation Study" Published in Nutrients, Publisher MDPI, IF: 6.706

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The PDF of this manuscript can be found in Appendix Section C (ii): Thesis-related Publications

1.1 Introduction

Vitamin D is a fat-soluble pre-hormone that is intrinsic for physiological health. It is known as the sunshine vitamin, as up to 90% of its source is supplied from the action of sunlight on exposed skin. It is considered to be the oldest hormone and was intrinsic in the development and calcification of the mammalian skeleton required for evolution of sea-dwelling animals onto land [6]. The importance of vitamin D production is evident from human evolution, whereby the migration of hominids away from the equator resulted in a selection for lighter skin tones, providing increased efficiency at lower ultraviolet (UV) intensities [7].

Due to its involvement in calcium and phosphorus homeostasis, maintaining adequate vitamin D is essential for bone health [8]. Vitamin D deficiency in childhood results in bone deformities, known as rickets [9]. Lack of vitamin D during the life course is also a risk factor for bone demineralisation, resulting in osteomalacia, and brittle bones, termed osteoporosis, in later life [10].

The awareness of vitamin D and its importance for bone health was not discovered until the 1920s, when rickets was found to be cured and prevented by two methods, via dietary sources (in the form of cod-liver oil) and via sunlight exposure. Eventually, due to the anti-rachitic properties of UV irritated foods, a greater understanding of the dual mechanism of vitamin D and its precursors was realised. This supported the hypothesis of the importance of vitamin D in bone health and led to the eradication of rickets in Western countries [11]. More recently, the role of vitamin D in other physiological processes has been investigated, with links to cardiovascular, immunological, inflammation, and respiratory health, however these are yet to be confirmed [8, 12].

This had led to an exponential increase in publications in the last twenty years, over and above that of the other vitamins [13]. This has consequently led to an increased public awareness and demand for vitamin D testing and repeat testing, at-times inappropriately, resulting in excess costs [14-16].

1.1.1 Vitamin D Metabolism

Vitamin D is unique as technically it is not a vitamin, but secosteroid hormone that is synthesised via the action of Ultraviolet-B (UVB) light on the skin, forming cholecalciferol (vitamin D_3) (Figure 1.1) [9]. While this is the predominant physiological source of vitamin D, it can also be obtained directly from the diet via animal sources and ergocalciferol (vitamin D_2) from plant sources, particularly mushrooms [10, 17].

When skin is exposed to UVB light at the correct wavelength (290-315 nm), the hormone precursor 7-dehydrocholesterol is converted from pre-vitamin D into vitamin D_3 [17]. Both vitamin D_2 from the diet and D_3 from diet and cutaneous synthesis are bound by a vitamin D binding protein (VDBP)

and transported to the liver [9]. Here it undergoes its first hydroxylation by the action of 25-hydroxlyase (CYP2R1) to form 25-hydroxycholecalciferol (25(OH)D; calcidiol), which serves as the primary circulatory form of vitamin D [18]. Approximately 85% of total 25(OH)D is bound to VDBP, with a further 15% bound to albumin and less than 0.1% remaining as free [19]. For the most part, unbound 25(OH)D enters cells, whereas in others such as the kidney, the parathyroid gland and placenta, VDBP serves as the mediator of 25(OH)D into the cell [19]. Calcidiol (25(OH)D) undergoes further 1∝hydroxylation in the kidneys by the enzyme 1-alpha-hydroxylase (CYP27B1) to form the active 1,25 dihydroxycholecalciferol ($1,25(OH)_2D$; calcitriol) [17]. Vitamin D synthesis is tightly controlled, whereby decreasing blood ionised calcium serum concentrations signal the parathyroid gland to increase parathyroid hormone (PTH) production, stimulating upregulation of CYP27B1 and increased $1,25(OH)_2D$ production in the kidneys [17]. Vitamin D receptors (VDR) have a high affinity for $1,25(OH)_2D$ and are ubiquitous in cells associated with calcium and phosphorus homeostasis [8]. Thus elevated $1,25(OH)_2D$ allows for the increased absorption of calcium from the intestines, and distal renal tubules to maintain normocalcaemia [9]. Vitamin D receptors have also been discovered in extra-musculoskeletal sites including immune cells neurones, in cardiac, respiratory, and other tissues where $1,25(OH)_2D$ may exert its effect [8]. When serum calcium concentrations stabilise, a negative feedback loop is initiated whereby $1,25(OH)_2D$, in addition to fibroblast growth factor (FGF-23), inhibits CYP27B1 and hence 1-alpha-hydroxylation and PTH secretion [18]. It also induces the expression of the enzyme 24-hydroxylase encoded by the CYP24A1 gene in the kidneys. This catalyses the conversion of 25(OH)D and $1,25(OH)_2D$ into the inactive 24-hydoxylated products, $24,25(OH)_2D$ and $1,24,25(OH)_3D$ respectively. Vitamin D is stored in the liver, muscle, and adipose tissue as 25(OH)D [17].

During pregnancy, vitamin D metabolism is upregulated considerably, with enhanced intestinal calcium absorption and calcitriol concentrations increasing up to three-fold in the first few weeks of gestation [20]. This contributes to increased availability of maternal 25(OH)D which crosses the placental barrier and facilitates the building of fetal vitamin stores. Furthermore, there is a considerable increase in maternal VDBP, both systemically and in the placenta, indicating it plays a crucial role in the immunomodulation of the maternal-fetal interface [20].

1.1.2 Measurement of Vitamin D Status

Due to the limited half-life of the biologically active $1,25(OH)_2D$ (4-6 hours) and its tight feedback control, nutritional vitamin D status is assessed by monitoring circulating concentrations of 25(OH)D, whose half-life is 3-4 weeks and under no feedback regulation [21]. There are several types

of vitamin D analytical techniques, with varying sensitivities and specifications [22]. These include binding assays; such as radioimmunoassay (RIA), chemiluminescence immunoassay (CIA), protein-binding assay (PBA), bioanalytical assays such as high-performance liquid chromatography (HPLC) and liquid chromatography tandem mass-spectrometry (LC-MS/MS). The accuracy of the binding assays will depend on the specificity of the protein utilised, though they are relatively quick and inexpensive. However, they are subject to interference from other vitamin D metabolites and may overestimate 25(OH)D concentration [21]. Bioanalytical assays allow for the quantification of a large number of samples, however they require more technical skill [22]. HPLC, previously the preferred method of 25(OH)D analysis, requires an additional step prior to chromatography and can experience interference [22]. LC-MS/MS is now considered the gold standard of vitamin D assessment and allows for the measurement of both $25(OH)D_2$ and $25(OH)D_3$ [21]. In order to improve the accuracy and repeatability of vitamin D assessment, the Vitamin D Standardisation Programme (VDSP) and Vitamin D External Quality Assessment Scheme (DEQAS) were developed and implemented [23, 24].

There has been a global surge in vitamin D testing, attributed to the increased coverage of media and a greater awareness in the public [14]. This is reflected in Ireland, where there has been an exponential increase in testing, and thus expenditure, over the last ten years [16, 25]. Currently, HSE guidelines for General Practitioners' state that testing should be limited to investigations for metabolic bone disorders, malabsorption conditions, unexplained musculoskeletal symptoms, liver disease and patients on certain medications [26]. It advises against routine testing of asymptomatic patients and has no guidance on when and whom to retest [26]. Elsewhere, inappropriate testing for non-clinical indications is common, with fatigue cited in up to 30% of referrals in the UK [27]. Similarly, repeated testing within insufficient time frames has been reported [28]. Despite the increased frequency of vitamin D testing, there has been no research to-date in Ireland investigating the indications for testing and the frequency of retesting. Data on this could help inform strategies to limit non-essential tests, and its associated costs.

1.1.3 Vitamin D Cut-Offs

The role of vitamin D in bone and muscle health is well established, however controversy remains over the optimal vitamin D thresholds for other potential health outcomes. Currently the National Academy of Medicine (NAM), (previously known as the Institute of Medicine (IOM)) defines deficiency as <30 nmol/L, with the Endocrine Society setting a higher value of <50 nmol/L [29, 30]. Contrary to this, the Scientific Advisory Committee on Nutrition (SACN) have defined deficiency

as a level below 25 nmol/L [8]. There is also the concept of insufficiency and replete or sufficient status which is usually defined as between 30 and 50 nmol/L [29]. A summary of recommendations is shown in Table 1.1.

There is no agreement on what constitutes an excessive or high 25(OH)D, with 125 nmol/L set by the NAM as suspected as harmful to health [29]. Levels above this have been associated with increased risk of falls and depression in some studies, as well as a potential U-shaped relationship with other outcomes [31]. Hypercalcaemia, defined as a serum calcium concentration greater than 2.75 nmol/L, is considered the indicator for vitamin D toxicity, presenting as nausea, fatigue, poor appetite, polyuria, and confusion [8, 32]. However, overt vitamin D toxicity that gives rise to hypercalcaemia is rare and does not usually occur until 25(OH)D levels are in excess of 300 nmol/L [30]. As a result of the lack of global consensus, the different cut-offs used in the research literature sometimes means that making comparisons between studies is difficult.

Furthermore, based on the known benefits for musculoskeletal health, many agencies have established different recommended dietary requirements for vitamin D. These have been estimated at the level at which 97.5% of the population may achieve adequate intake to protect health, with some choosing the prevention of deficiency (<25 nmol/L) [8], with others basing these recommendations on achieving sufficiency (>50 nmol/L) [29, 33, 34]. As a result, dietary recommendations vary between 10-15 μg /day, with higher levels recommended in individuals with limited sun exposure. However there remains controversy, with suggestions of a miscalculation of the appropriate level of intakes to avoid deficiency [35]. Indeed, modelling studies in the Irish population has estimated between 25 and 28 μg /day is the required level to maintain wintertime sufficiency (>50 nmol/L) in adults and older adults [36, 37]. Despite this, recommendations in Ireland were recently updated, with those age 12-65 years now advised to intake 15 μg /day in order to maintain serum 25(OH)D >30 nmol/L [4].

While cutaneous synthesis of vitamin D_3 is tightly regulated and so cannot result in the excess production high oral or intravenous intakes can have adverse effects. As such a Tolerable Upper Intake Level, the level at which daily intake is not thought to cause harm, has been set by the NAM at 100 μg/ 4000 IU for adults and pregnant women, 25 μg /1000 IU for infants (<6 months) and 38 μg /1520 IU for infants (6-12 months) [29]. Similarly, the European Food Safety Authority also set a limit of 100 μg/4000 IU per day for adults and children (11-17 years), with 50 μg /2000 IU designated for children aged 1-10 years [33]. Based on existing data, it is unlikely hypercalcaemia occurs at

intakes below 250 μg/ 10,000 IU/day, considered the No Observed Adverse Effects Level (NOAEL), the highest level no valid, published effects have been found [8, 38], with intakes >1250 μg/ 50,000 IU for several months required for toxic side-effects [38].

Table. 1.1 Serum 25(OH)D Recommendations

Report	Location	Deficiency level	Sufficiency Level
NAM 2011 Report [29]	USA	<30 nmol/L	>50 nmol/L
Endocrine Society Clinical Practice Guidelines 2011 [30]	USA	<50 nmol/L	>75 nmol/L
Nordic Nutritional Recommendations Report 2012 [34]	Nordic Countries		>50 nmol/L
SACN 2016 Report [8]	UK	<25 nmol/L	
EFSA 2016 Report [33]	EU		>50 nmol/L

NAM; National Academy of Medicine, SACN; Scientific Advisory Committee on Nutrition,
EFSA; European Food Safety Authority

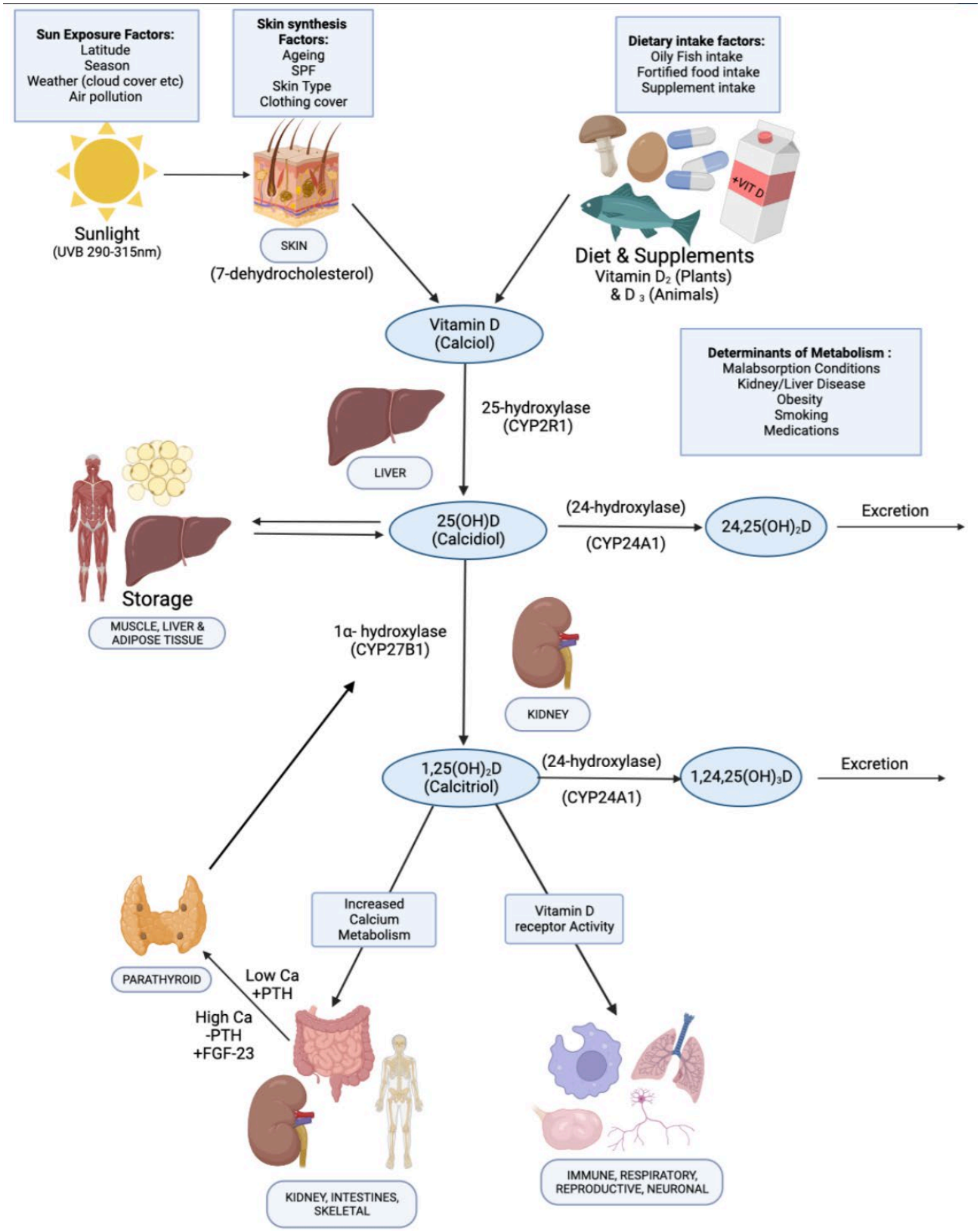


Figure 1.1 Vitamin D Metabolism

1.1.4 Importance for Bone Health

Vitamin D is crucial for musculoskeletal health, being essential for the adequate absorption of calcium from the gastrointestinal tract. Deficiency can result in secondary hyperparathyroidism in adults, lead to the osteomalacia and contribute to the development of osteoporosis [8]. In children vitamin D deficiency can lead to rickets, a condition caused by poor calcium and phosphate absorption leading to under-mineralisation of the bones. It is characterised by deformation of the long bones, resulting in 'knock knees' or 'bow-legs' and can also cause ribcage collapse and pelvic malformation [9]. During adolescence, another period of extensive bone growth, inadequate vitamin D can result in aches and pains, and muscle weakness [39]. Sufficient vitamin D stores at this time are crucial for reaching peak bone mass. Osteomalacia in adults, like rickets in children is caused by the de-mineralisation of bone owing to a chronic lack of vitamin D and calcium, and alterations in phosphate homeostasis. This results in poor calcium absorption and can cause deterioration in bone microarchitecture and increased fracture risk [9].

1.1.5 Implications for Non-Musculoskeletal Health

While its function in bone and muscle health is well known, the discovery of vitamin D receptors (VDRs) in numerous human cells has led to the exploration of its effects in other physiological functions. VDRs have been identified in vascular and cardiac smooth muscle, with vitamin D deficiency linked to hypertension, stroke, myocardial infraction, and all-cause mortality [7]. Vitamin D is thought to serve as an immunomodulator due to its ability to affect both the innate and adaptive immunity via cytokine secretion and regulation of cell signalling pathways, with VDRs identified in macrophages, lymphocytes, and dendritic cells [40]. As such vitamin D has been identified in the elimination of invasive pathogens, and the suppression of the harmful effects of chronic inflammation [41, 42]. More recently, in signalling of anti-inflammatory molecules and down-regulation of pro-inflammatory has led to investigations of its role modulating 'cytokine storms', a condition associated with COVID infections [43].

In addition to the renal conversion of 25(OH)D to the active 1,25(OH)D, many other cells in various tissues such as the prostate, colon, breast, thyroid, gastrointestinal, brain and skin have shown this capacity [44, 45]. As such vitamin D deficiency has been linked to inflammatory bowel conditions such as Crohn's disease and ulcerative colitis, cancer prevalence and mortality, autoimmune conditions including type 1 diabetes, and respiratory conditions such as asthma [12, 41, 45]. While plausible physiological mechanisms for the effects of vitamin D on extra-skeletal health exists, with some

supporting evidence from observational trials, evidence from robust randomised control trials is limited and as such cannot be confirmed [8, 45].

1.1.6 Determinants of Vitamin D

1.1.6.1 Biophysical Factors

Aging

Age affects the production of vitamin D, due to biological and physical changes. There can be limited exposure to the sun, especially for institutionalised or home-bound individuals, and reduced dermal capacity of 25(OH)D production [46]. It is estimated that the vitamin D production of a 70-year-old is roughly 75% than of a twenty-year-old at the same latitude [47]. Dietary vitamin D may also be hindered due to intestinal malabsorption and a reduced intake in the diet [48]. As a result of this, older adults are considered at increased risk of vitamin D deficiency and are advised by the Food Safety Authority of Ireland (FSAI) to receive a daily supplement of 15 μg (600 IU) throughout the whole year [3].

Ethnicity

Individuals with dark skin types are at increased risk of vitamin D deficiency, as a higher melanin content reduces the cutaneous production of vitamin D_3 by limiting the action of UVB on skin. It is estimated that those with lighter skin types require 9-13 minutes of daily sun exposure during March-October with season appropriate clothes, with those of darker skin types requiring 25-40 minutes, to achieve an end of summer concentration of approximately 80 nmol/L [49]. As such there are numerous observational studies that have detected low vitamin D status in those with dark skin types at the same latitude [47, 50].

Cultural practices of certain ethnic populations also contribute to the prevalence of vitamin D deficiency. The religious custom of total or near total covering of the skin (hijab or niqab), severely limits sun exposure and strongly correlates with vitamin D deficiency in the Middle East and Africa [47]. In South Asia, it is more culturally common to conceal skin than in Europe or Americas. Additionally, sun avoidant practices are more prevalent in these populations due to the extreme heat [47]. Therefore, those of darker skin types and who have a high degree of clothing coverage are considered at risk of vitamin D deficiency [29].

Despite the increased risk of vitamin D deficiency in ethnic minorities, particularly those living in northern locations, there is a dearth of information in Ireland. Just one study has solely focused on establishing prevalence of vitamin D deficiency in an immigrant population in Ireland, finding the majority (67%) of Southeast Asians were deficient [51]. Several cross-sectional studies have found that non-Caucasian pregnant women and children had significantly lower vitamin D status, however the samples were small (n<100) [52-54]. Increased risk of vitamin D deficiency in those with non-Caucasian ethnicity living in Northern Europe has been confirmed elsewhere [55-57].

Obesity

As lipophilic 25(OH)D is sequestered in adipose tissue, those with increased adiposity /obesity, defined as a Body Mass Index (BMI) greater than 30kg/m^2, are at risk of lower serum concentrations [58, 59]. This is likely due to a reduction of vitamin D that is available for 1α-hydroxylation in the kidneys [29]. Previous studies have shown that a reduction in body fat, with no change in dietary intake or sun exposure, increased rates of circulatory 25(OH)D [60, 61]. In addition, increased adiposity has been negatively correlated to response to vitamin D supplementation [61, 62]. As such, body mass should be considered when advising for supplement use to maintain sufficient 25(OH)D concentrations [58, 62].

Sex

Studies into the effect of sex on vitamin D status are largely inconclusive, with some large meta-analysis showing no effects [63], with others indicating that females are at increased risk of low vitamin D [47, 64]. The conflicting evidence may reflect differences in lifestyles and biophysical factors between males and females. In particular, women of Middle East/ Africa and Asian/Pacific regions are particularly vulnerable due to cultural practices of clothing cover, reducing opportunity for sun exposure and skin synthesis of vitamin D [63, 64]. In addition, pregnant and breastfeeding women are known to be at risk of vitamin D deficiency [65, 66]. Conversely, women are more than twice as likely to habitually take vitamin supplements [67, 68], and due to the emphasis on osteoporosis, are more likely to be aware of the importance of bone health [69].

Chronic disease

Malabsorption conditions such as Inflammatory bowel, Crohn's and Coeliac disease decreases the absorption of vitamin D from the intestines and can lead to deficiency [70]. Between 19-70% of children and adults with Crohn's disease are known to have 25(OH)D concentrations less than 50 nmol/L [71]. Vitamin D deficiency is not only prevalent in patients with Coeliac disease [72], but may

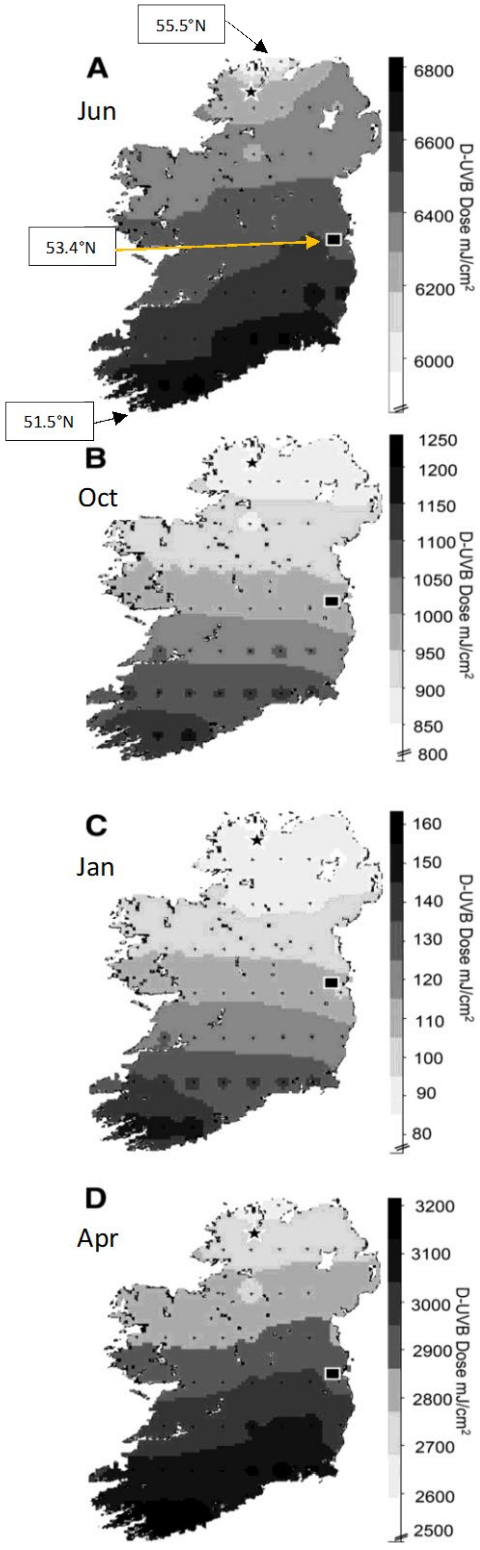
play a role in the pathogenesis of the condition due to its increased prevalence in children born in the summer [73]. Renal disease causing nephrotic syndrome is associated with vitamin D deficiency [74]. Chronic liver disease causes a reduction of vitamin D 25-hydroxylation and VDBP production. 25(OH)D levels below <50 nmol/L has previously been detected in up to 62-93% of chronic liver disease patients, with increasing prevalence with disease progression [75].

1.1.6.2 Lifestyle Factors

Sunlight Exposure

Sunshine exposure is the most effective method for vitamin D production, however as Ireland sits between 51 and 55° North, opportunity for synthesis is limited for the majority of the year, leading to a high risk of deficiency [76-78] (Figure 1.2). Exposure of the arms and legs for 5-15 minutes per day between spring and autumn, and between 10am and 3pm will provide sufficient vitamin D for a Caucasian skinned adult [76]. Approximately 90% of vitamin D is obtained via cutaneous synthesis, however this is dependent on numerous factors [17]. The availability of sunlight is largely based on the latitude, with those at greater than 35°N, having a limited seasonal period at which sufficient vitamin D can be made [17]. In Ireland, cutaneous vitamin can only be synthesised when UVB light is at the correct wavelength (290- 315nm) between March and October [17]. In addition to season, time of day, weather (such as cloud cover), pollution, clothing cover, and sun protection factor will determine cutaneous UVB exposure and vitamin D_3 that can be produced [17, 76, 78, 79].

Sun enjoyment has previously been found to be a predictor of vitamin D status in older Irish adults [78]. In a sample of northern European women and girls, sun seeking was a positive predictor of vitamin D status and in Irish females [80]. Previous research has suggested that sunscreen largely prevents vitamin D synthesis [81], however recent studies suggests that its effect may be much lower than previously thought [82, 83].



The star (★) denotes Derry, and the square (▪) denotes Dublin. D-UVB, daily ambient Ultraviolet (UVB) dose at wavelengths that can induce vitamin D synthesis. Adapted from O'Sullivan et al., (2017) [78].

Figure 1.2 Vitamin D - UVB on the Island of Ireland

Diet

As a result of the limited and variable nature of vitamin D production by sun exposure there is a dependence on dietary sources. The richest sources include oily fish, egg yolk, sun ripened mushrooms, and fortified products including dairy and spreads (See Table 1.2). However, the contribution of dietary sources is small and obtaining sufficient daily levels is difficult, with up to 97% of the adult Irish population not meeting recommended intakes of 10 μg (400 IU) [84]. Despite its relatively small vitamin D content, the main contributors of dietary vitamin D in Irish adults (18-64 years) are meat (30%), followed by fish (12%) and fortified spreads (10%) and eggs (9%). Similarly, meat and meat products are the largest contributor to vitamin D status in teens (29%), followed by fortified breakfast cereals (19%), fish (11%) and milk & yogurt (11%) [85]. In children aged 1-5 years, breakfast cereals are the greatest source of vitamin D (23%), followed by meat & meat product (20%), and milk & yogurt (17%) [86]. While a number of food products, including dairy and cereals, are fortified with vitamin D on a voluntary basis, no mandatory fortification policy exists [3]. A summary of the main sources of vitamin D in the Irish population is shown in Figure 1.3.

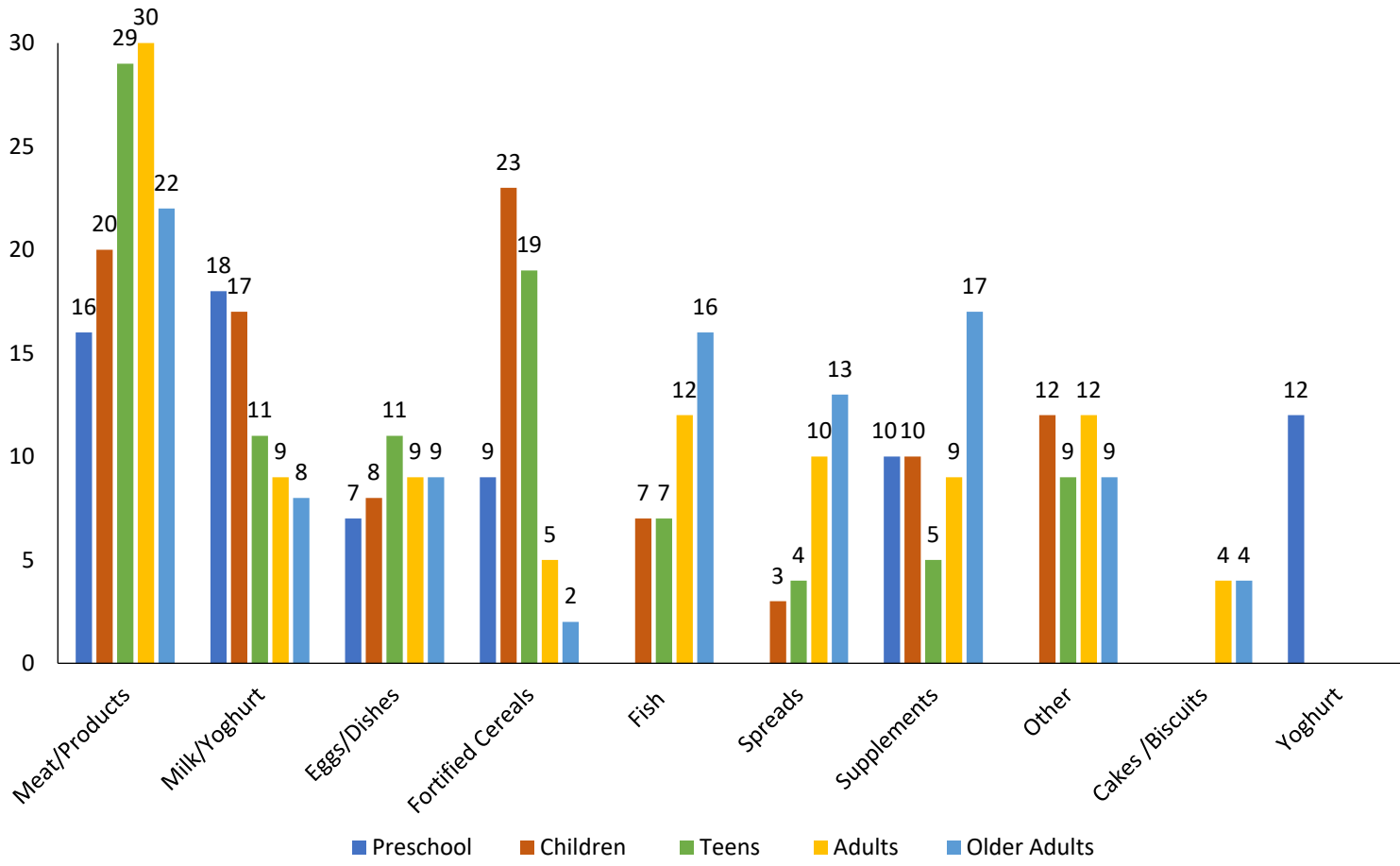
The maintenance of adequate intake and status is essential for children and adolescents, as these are periods of intensive growth, during which demands for vitamin D may increase [87]. Up to 90% of peak bone mass is attained during this time, with failure to maximise this resulting in increased risk of osteoporosis in later life [88]. In a recent large investigation, nearly half of children/adolescents had insufficient (<50 nmol/L) vitamin D status, with a higher prevalence in older children [89]. Similar findings have been identified in the UK, with females, non-Caucasian, and those from low-socioeconomic status most at risk [90].

Dietary intake of oily fish and fortified milk consumption has been associated with better vitamin D status in frail older Irish adults [46]. However, there has been little evidence on compliance with dietary recommendations and no investigation to-date on awareness of vitamin D Recommended Dietary Allowance (RDAs). Previously it has been found that knowledge of vitamin D predicted supplement use in the EU [91, 92]. As such improving knowledge of the recommendations could help increase compliance in the population.

Table 1.2 Vitamin D Content of Foods

Food Sources	Vitamin D (per 100g/100ml)
Fish	
Herring, grilled	16.1 μg/ 644 IU
Salmon, smoked	8.9 μg/ 356 IU
Wild Salmon, fresh	8.6 μg/ 344 IU
Mackerel, grilled	8.5 μg / 340 IU
Rainbow Trout, baked	8.2 μg/ 328 IU
Mackerel, canned	7.4 μg/ 296 IU
Farmed Salmon, fresh	4.7 μg/ 188 IU
Sardines, fresh	4 μg/ 160 IU
Sardines, tinned in brine	3.6 μg/ 144 IU
Tuna, grilled	3.1 μg/ 124 IU
Tuna, tinned in brine	1.1 μg/ 44 IU
Dairy Products	
Supermilk©, (Whole or Low fat)	2 μg/ 80 IU
Actimel©	1.7 μg/ 68 IU
Animal Products	
Eggs, chicken	3.2 μg/ 128 IU
Corned Beef, canned	1.3 μg/ 52 IU
Sausages, pork, grilled	1.1 μg/ 44 IU
Pork loin	0.8 μg/ 32 IU
Roast Beef	0.8 μg/ 32 IU
Roast Pork	0.7 μg/ 28 IU
Bacon rashers	0.6 μg/ 24 IU
Non-Animal Based	
Kellogg's© Cereal	8.4 μg/ 336 IU
Benecol©/ Flora© Spread	7.2 μg/ 288 IU
Sun-ripened Mushrooms	7 μg/ 280 IU
Low Low© Spread	5 μg / 200 IU
Other Fortified Cereal	3.9-5 μg / 156-200 IU

Reference: Composition of Foods Integrated Dataset including McCance and Widdowson 7th edition, 2015 [93]



Data as reported in Irish Universities Nutrition Alliance (IUNA) reports [85, 94-96]

Figure 1.3 Dietary Sources of Vitamin D in the Irish Population

Supplement Use

Infants less than 1 year who are breastfed or consuming less than 300ml of infant formula per day are advised to receive a supplement of 5 µg (200 IU)/day [1]. Children between 1 and 5 years are recommended to receive 5 µg (200 IU)/ day, supplementing, if necessary, between October and March [2], with older children (age 6-11 years) advised to consume 10 µg/day [2, 4]. Adults and adolescents over 12 years are advised to maintain a vitamin D intake from food and supplements of 15 µg (600 IU)/day, with adults over 65 advised to take 15 µg (600 IU) [3], increasing to 20 µg (800 IU) if housebound with little access to sunlight [3, 4] (Figure 1.4).

However, adherence is poor, with 94% of children and 85-97% of adults failing to meet the Recommended Dietary Allowance (RDA) at the time (10 µg/day) [84, 97].

Supplement use has been found to be predictive of levels >30 nmol/L in children [54], pregnant women [52] and older adults [46, 48], yielding a significant improvement in vitamin D status [54]. A positive association of supplement use and vitamin D status has also been found in athletes [98, 99]. In a cross-sectional analysis of two large studies of older Irish adults, it was the strongest predictor of vitamin D status [46, 48]. Supplements were responsible for 17% of intake in older adults (>65 years) versus 9% in adults aged 18-64 [94]. Additionally, vitamin D supplements contributed more to intake than diet, with women having a greater proportion of intake from supplements than men, who consumed more dietary vitamin D [68]. Despite recommendations, supplement consumption is low in the Irish population, with just 10-23% of children [54, 86, 97], and 10-28% in adults [43, 84] consuming any vitamin D, with adolescents and younger adults having lower rates [84, 100]. However, since the successful introduction of the vitamin D supplementation policy in infants [1], adherence to supplementation now ranges at 93% at 2 months to 72% at 12 months [101].

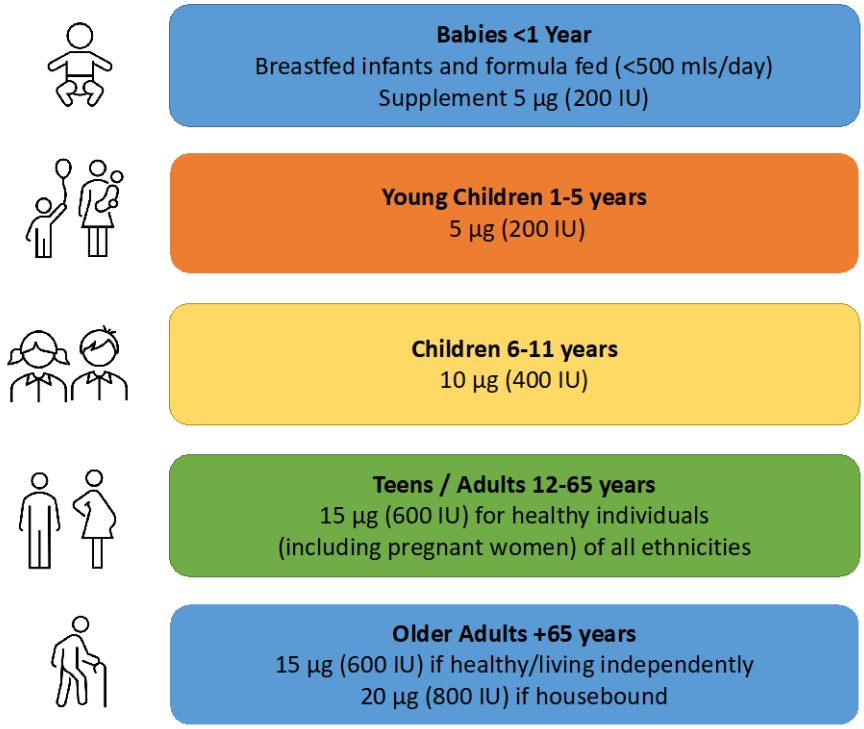


Figure 1.4 Irish Vitamin D Recommendations by Age Group [1-4]

Socioeconomic Status

Socioeconomic status (SES) acts as an indirect determinant of vitamin D status due to its influence on a number of factors. Diet quality and variety is associated with SES, with educational attainment being a key driver of a healthy diet [56]. A healthier lifestyle has been found to be associated with a

higher vitamin D status [102]. In particular, lower SES is linked to lower rates of fish consumption and supplement intake, and potentially less access to sun holidays, and thus lower vitamin D status [48, 103]. Increased prevalence of obesity, smoking and reduced access to outdoor amenities and lower education attainment can also contribute to reduced status in those of poorer backgrounds [47, 48, 104-106].

In Ireland, the effect of socioeconomic status on vitamin D status has seldom been explored. In older adults, lower asset wealth was associated with deficiency prevalence [48], with social economically deprived adults in urban locations having highest levels [25]. Young, disadvantaged women were also significantly less likely to meet the recommended dietary intakes of vitamin D [107]. No studies have investigated the effect of SES on vitamin D status in children, with others relying on proxy measures including education level or private health insurance [54, 108]. Socioeconomic deprivation has previously been associated with reduced dietary intake and deficiency in other northern European countries [55, 109]. As such those of low socioeconomic status should be considered at increased risk of vitamin D deficiency and warrant further investigation.

Smoking

Smokers have previously been found to have higher rates of vitamin D deficiency [48, 110]. Smoking disturbs a number of pathways in the physiological generation of vitamin D. It promotes skin aging and disrupts cutaneous synthesis by 7-dehyrodrocholesterol [111]. It may also reduce the availability of $1,25(OH)_2D$ by the reduction of PTH, downregulating the expression of CYP27B1, increasing renal disruption, and increasing the catabolic enzyme 1,25OHD,24-hydroxylase (CYP24A1) [111]. In addition, smoking may serve as a surrogate marker of an unhealthy lifestyle including a poor diet, alcohol consumption and less physical activity, leading to reduced sun exposure and thus vitamin D synthesis [110].

1.1.7 Importance in an Irish Context

Due to limited sun exposure, the Irish population is dependent on dietary sources of vitamin D, however intakes remain low, and most of the population do not meet the recommended daily amount. In addition, the proportion in the population at-risk of vitamin D deficiency is rising due to several demographic changes, with an increase in rickets incidence observed [2]. The population is ageing, with the number of people over 65 set to double by 2050 [112]. Overweight and obesity is also markedly increasing, at 60.6% and 25.3% in 2016 respectively, up from 54.8% and 19.3% in 2006 [113]. There has also been a large increase in the proportion of the population with an ethnicity

other than Caucasian Irish [114]. The ethnic population has been found to be at greater risk of vitamin D deficiency, with a recent study indicating 93% of South-east Asians in Ireland had insufficient vitamin D concentrations [51].

To-date much research has focused on establishing vitamin D status and its determinants in older adults and only in some at-risk populations, including those with malabsorption conditions. Despite growing research on vitamin D in Ireland, no review has comprehensively examined vitamin D research conducted in Northern Ireland and the Republic of Ireland. As such this review aims to collate the vitamin D research undertaken on the island of Ireland, with regard to studies of vitamin D status, intake, and supplementation/intervention trials in various population groups in Ireland.

1.2 Methods

A literature search was conducted using the EMBASE database and Google Scholar to identify original research published in the Republic of Ireland and Northern Ireland between 1990 and 2022. Observational studies (cross-sectional, retrospective, and longitudinal) and randomised controlled trials, with access to full text and published in peer-reviewed journals were considered. The search string for EMBASE was ‘'vitamin’':ti,ab,kw OR colecalciferol:ti,ab,kw OR’'25oh’':ti,ab,kw OR 25:ti,ab,kw) AND oh:ti,ab,kw AND d:ti,ab,kw AND19hildred:ca AND {1990-2022}/py AND’'huma’'/de AND’'Articl’'/it. The search term for Google Scholar was vitamin D* OR 25(OH)D AND Ireland. Articles were screened based on their title and abstract against pre-determined criteria to determine their suitability. Only articles meeting the selection criteria below were included:

1) Original research published between 1990-2022
2) Studies in humans
3) Research participants on the island of Ireland (Republic and Northern Ireland)
4) Studies reporting total serum 25(OH)D, vitamin D intake and supplementation/intervention trials
5) Articles published in English in peer-review journals with access to full text
6) Nationally representative reports on vitamin D status/intake.

This review was conducted based on framework for scoping reviews recommended by Arksey & O’Malley (2005) [115], and later improvements to this method [116, 117]. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed using the PRISMA extension for scoping reviews checklist (Figure 1.5). Two reviewers (H.S & E.L) performed searches and independently identified articles for inclusion. A collection of papers identified by each reviewer was compared for consistency, with discussion of papers of ambiguous eligibility.

Of the 349 articles identified, 250 were screened for suitability after removal of duplicates. Of these, 59 were excluded as they were not peer reviewed and 2 could not be retrieved leaving 189 articles. An additional 47 did not meet other inclusion criteria leaving 142 articles and 7 nationally representative reports. Study types included observational (cross-sectional, case-controlled, retrospective, and prospective) (n=107), randomised controlled trials (n=27), and vitamin D population modelling (n=8).

For the purpose of this review, deficiency was defined as serum 25(OH)D <25 nmol/L or <30 nmol/L depending on the study and vitamin D excess >125 nmol/L. Studies reporting total serum 25(OH)D and/or vitamin D status were categorised by population tested. Vitamin D status reported as ng/mL were converted to nmol/L using the multiplier factor 2.5. We defined older adults as those >50 years, and those at-risk to include malabsorption conditions (for example Crohns disease) and non-Europeans. We also included any studies that reported associations between vitamin D and medical conditions.

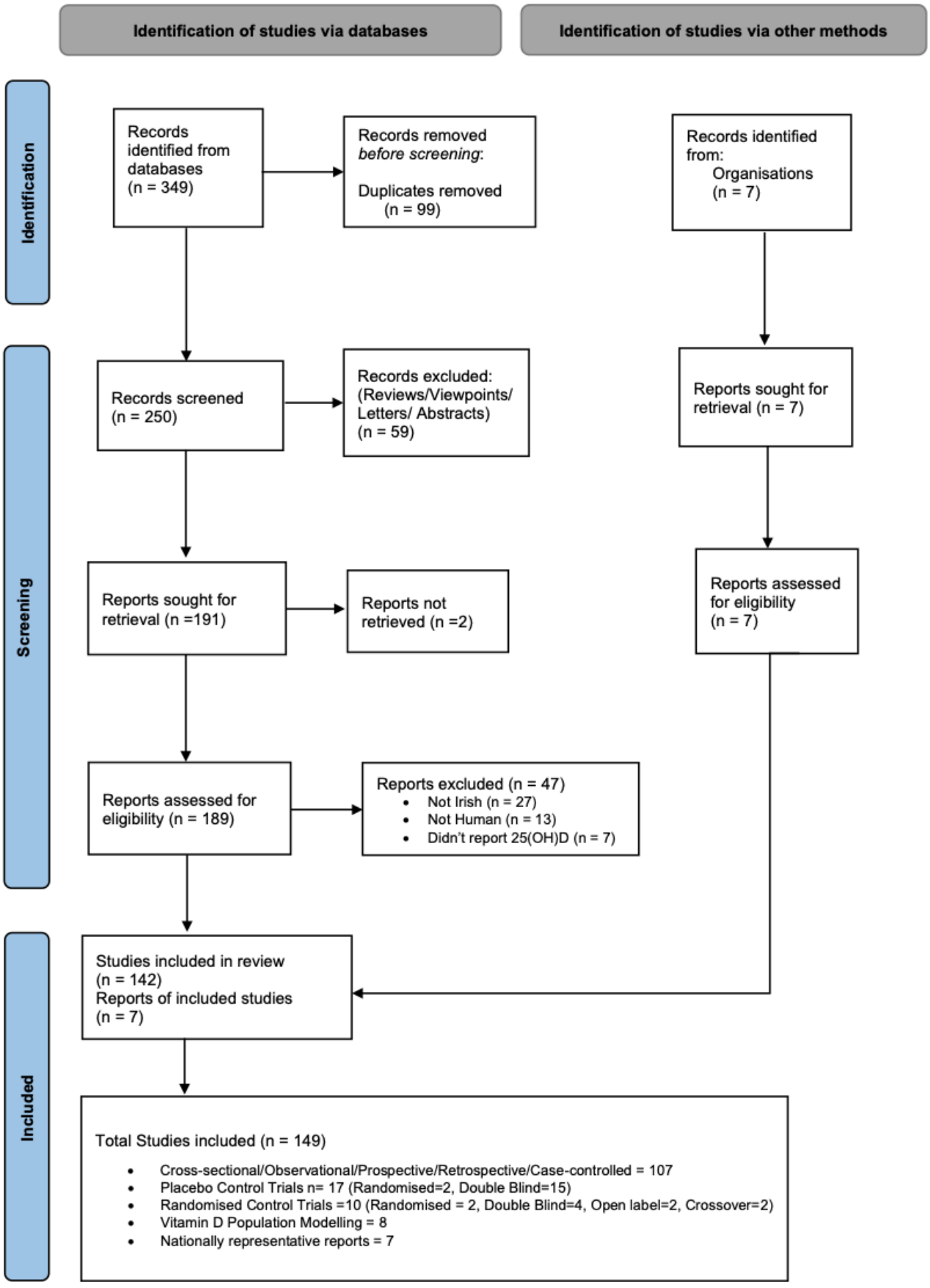


Figure 1.5 PRISMA (2009) Flow Diagram [5]

1.3 Results

Studies reporting vitamin D status/intake in pregnancy (n=19) area are outlined in Table 1.3, childhood (n=14) in Table 1.4, adult (n=16) in Table 1.5, older adult (n=19) in Table 1.6, at-risk population (n=23) in Table 1.7 and dietary studies (n=17) in Table 1.8. The majority of studies have been in at-risk groups (n=28), and older adults (n=23), with only 17 studies in children.

1.3.1 Vitamin D Status by Population Categories

- **Fertility/ Pregnant Women (n=19)**

We identified 1 study in fertility and 18 in pregnancy (Table 1.3). The largest investigation in pregnancy (n=1796) found 17% were deficient, with most ranging between 13-61% [52, 53, 118]. The study on vitamin D status and fertility identified that 18% of men and 19% of women undergoing fertility treatment were deficient, and a further 40-63% had levels <50 nmol/L with no correlation found with pregnancy outcomes [119]. In early pregnancy (12-16 weeks' gestation), deficiency ranged between 13%-29% [52, 53, 118, 120-127] with rates increasing with gestation in most [120, 121, 124, 127] but not all [128] studies. A seasonal variation in vitamin D deficiency in pregnancy was found [53, 118, 122, 124, 128-130], with the lowest prevalence of 3-7% detected in summer/autumn [53, 118]. A high proportion of mothers (25-65%) were deficient at delivery [131, 132], though in one study only 2% were deficient (<25 nmol/L) at 3 days postpartum though samples were taken in Autumn [128].

Serum 25(OH)D <50 nmol/L ranged from 7-96%, and in larger studies (n>100) were between 42-83% [52, 133], and was greater with increasing gestation [120, 124]. A seasonal effect was also evident, with up to 96% of mothers having levels below 50 nmol/L in both winter and spring in one study [128]. In contrast, only 13% had levels <50 nmol/L in Autumn in one report [128].

A lower risk of pre-eclampsia and small for gestational age (SGA) babies was detected in pregnant Irish women with vitamin D >75 nmol/L [53]. While low vitamin D status in early pregnancy in Irish women was linked with increased fasting glucose and Homeostatic Model Assessment. (HOMA) [121, 124]. In addition, low maternal 25(OH)D in early pregnancy was associated with increased risk of atopy in children at 2 years [127].

Table 1.3 Vitamin D status in Pregnancy and Fertility Studies in Ireland

Study	n	Supp Users	Location	Age	Gestation	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
		(%)	(°N)	(Years) Mean (SD)	(Weeks)	(µg/day) Mean (SD)	(nmol/L) Mean (SD)		(nmol/L)	(%)	(nmol/L)	(%)	
O'Riordan 2008 [122]	43	supp excl.	Cork (52)	22-41 (Range)	3 Trimesters	3.6 (1.9)			<25	14-24	<50	49-76	ELISA
					3 Trimesters		50.9 (23.4)	Light season (Apr-Sept)	<25	17	<50	58	
					3 Trimesters		32.2 (12.2)	Dark season (Oct-Mar)	<25	30	<50	91	
Holmes 2009 [128]	99	22	Belfast (54-55)	28.8 (5.6)	12			Winter (Dec-Feb)	<25	35	<50	96	ELISA
					20			Spring (Mar-May)	<25	44	<50	96	
					35			Summer (Jun-Aug)	<25	16	<50	75	
					3 days PP			Autumn (Sept-Nov)	<25	2	<50	13	
McCarthy 2013 [123]	274 (57% Male)		Dublin (53)		18 (11-28) days Median (Range)		39·4 (20·1–116·0) Median (range)	Jun 08-Jul 10	<30	14	<50	79	RIA
Walsh 2013 [121]	60	62%	Dublin (53°N)	N/a	Early 14.3 (2.3)	2.78 (1.8)	45.7 (22.5)	50% Summer/ 50% Winter*	<30	28	<50	61	RIA
					28 weeks		54.4 (33.4)			15		58	
					Cord		31.8 (12.5)			45		92	
Toher 2014 [52]	116	34	Dublin (53)	31 (27–34) Median (IQR)	14 (13–16) Median (Range)		25.9 (16.5–44.7) Median (Range)	Apr-May	<30	61	<50	83	PBA
Zhang 2014 [120]	30		Cork (52)	30.4 (3)	15		49.9 (16.5)	May-Sept	<30	10	<50	63	ELISA
					36		37.4 (22.0)		<30	53	<50	80	

Table 1.3 Vitamin D Status in Pregnancy and Fertility Studies in Ireland Continued

Study	n	Supp Users	Location	Age	Gestation	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
		(%)	(°N)	Mean (SD) (Years)	(Weeks)	Mean (SD) (µg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
Onwuneme 2015 [132]	94 Preterm (44% Male)		Dublin (53)		28.8 (2.1) Mean (SD)		22.8 (22.6)	Sept 11-Sept 13	<30	64	<50	92	PBA
	94 Mothers						27.1 (16.7)		<30	65	<50	91	
Kiely 2016 [53]	1796	40	Cork (52)	30.5 (4.5)	15		56.7 (25.9)		<30	17	<50	44	LC-MS/MS
							66.7 (24.3)	Summer (Jun-Oct)	<30	7	<50	26	
							49.6 (24.6)	Winter (Nov-May)	<30	25	<50	57	
Neville 2016 [119]	75 Male	53	Dublin (53)	37.4 (4.4)	n/a		51.7 (2.8)	Jan-Mar	<30	18	<50	40	PBA
	63 Female	63		36.5 (3.3)	n/a		47.4 (2.8)	Jan-Mar	<30	19	<50	63	
Onwuneme 2016 [131]	57 Infants (56% Male)		Dublin (53)		40.0 (1.8) Cord Mean (SD)		29.4 (14.8)	Winter (Dec-Apr) 84%	<30	63			RIA
	57 Mothers						42.8 (21.0)		<30	25			
O'Brien 2017 [124]	334	N/a	Dublin (53)	33.0 (3.9)	12		39.2 (27.2) *Median IQR	50% Winter (Nov-Apr)	<30	27	<50	61	PBA
								<30 Winter (Nov-Apr)	<30	39	<50	73	
								<30 Summer (May–Oct)	<30	16	<50	50	
					28		35.8 (27.3) *Median IQR		<30	33	<50	63	
								<30 Winter (Nov-Apr)	<30	34	<50	62	
								<30 Summer (May–Oct)	<30	33	<50	64	
Kiely 2017 [129]	1050 (51.6% Male)		Cork (52)	30.6 (4.3)	40.0 (1.4) (Cord)		34.9 (18.1)	50% Winter	<30	46	<50	80	LC/MS

Table 1.3 Vitamin D Status in Pregnancy and Fertility Studies in Ireland Continued

Study	n	Supp Users	Location	Age	Gestation	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
		(%)	(°N)	(Years) Mean (SD)	(Weeks)	(µg/day) Mean (SD)	(nmol/L) Mean (SD)		(nmol/L)	(%)	(nmol/L)	(%)	
	603						28.4 (15.2)	Winter (Nov-May)	<30	62	<50	88	
	447						43.6 (18.1)	Summer (Jun-Oct)	<30	24	<50	68	
McCarthy 2018 [133]	734	42	Cork (52)	31.0 (29.0, 33.0) Median (IQR)	15		58.3 (25.8)		<30	15	<50	42	LC-MS/MS
							67.0 (23.7)	Summer*					
							52.0 (25.5)	Winter*					
					40.4 (Cord)		35.1 (18.2)		<25	34	<50	80	
O'Brien 2018 [130]	205		Dublin (53)				Median (IQR)						CBA
	96	40%		33.0 (3.7)	13		21.8 (16.0-26.9)	Winter (Nov-Apr)					
						Median (IQR)	63.7 (56.8-76.1)	Summer (May-Oct)					
	109	42%		32.6 (4.3)	28	2.3 (1.7-2.9)	19.8 (15.1-25.5)	Winter (Nov-Apr)					
						2.5 (1.7-4.1)	69.6 (55.8-85.7)	Summer (May-Oct)					
O'Callaghan 2018 [118]	144	69	Cork (52)	Range 21-41	14		54.9 (22.6)		<30	13	<50	44	LC-MS/MS
								Winter (Nov-May)	<30	15	<50	56	
								Summer (Jun-Oct)	<30	3	<50	7	
Hemmingway 2018 [125]	142	68	Cork (52)	33 (4)	14 (2) Mean (SD)	10.7 (5.2)	54.9 (22.6)	78% Winter (Nov-May)	<30	13	<50	44	LC-MS/MS
Hemmingway 2018 [126]	1754	40	Cork (52)	30.5 (4.5)	15		56.6 (25.8)	58.4% Winter	<30	17	<50	44	LC-MS/MS
Smith 2020 [127]	279		Dublin (53)		13		41.9 (19.2)		<30	29			PBA
Alhomaid 2021 [134]	240		Belfast (54–55)										

Table 1.3 Vitamin D Status in Pregnancy and Fertility Studies in Ireland Continued

Study	n	Supp Users	Location	Age	Gestation	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
		(%)	(°N)	(Years) Mean (SD)	(Weeks)	(μg/day) Mean (SD)	(nmol/L) Mean (SD)		(nmol/L)	(%)	(nmol/L)	(%)	
	10 μg = 118	56		29.7 (5.1)	12		52.2 (22.9)	51.7% Winter (Oct-Mar)			<50	42	LC-MS/MS
	20 μg = 121	67		29.5 (5.5)	12		52.0 (20.5)	55.4% Winter			<50	49	

ELISA; enzyme-linked immunosorbent assay, LC-MS/MS; Liquid Chromatography with tandem mass spectrometry, PBA; Protein Binding Assay, PP; Postpartum, RIA; Radioimmunoassay, IQR; Interquartile Range. °N; Northern Latitude (Degrees). * Not defined.

- **Children/ Adolescents (n=17)**

Studies show that vitamin D deficiency is prevalent in Irish children occurring in up to 68% [135] (Table 1.4). In the largest investigation to date (n=5,524), 15% of children (5-20 years) were deficient [89], with the second largest (n=1,226) finding a deficiency rate of 23% [136]. Females generally had lower vitamin D status [54, 135-138], but not in all studies [139]. Some studies of children in summer found very low levels (<2%) of deficiency (<25 nmol/L) [137, 140, 141], with up to 20% in others [136].

Overall, there appeared to be a U-shaped pattern in deficiency prevalence by age, being lower in younger children and infants (<1 year) and greatest in adolescents. Most new-borns were found to have low vitamin D at birth, with deficiency in 34%-63% of cord blood samples [121, 129, 131, 133]. In preterm infants, 64% were deficient at delivery [132], with a prevalence of up to 14% at 12 days old [123]. In term infants, there was also a high level of deficiency ranging between 34-63% in most studies [121, 129, 131, 133]. Vitamin D status was generally better in younger than older children [54, 89, 136], with a large study finding a greater prevalence of deficiency in over vs. under 1's (24% vs. 16%) [136]. Lower rates of deficiency (2%) have been found in toddlers (aged 2 years) and children under 5 (13%) [139, 141], with higher 25(OH)D also reported in those under versus over 4 years (61.0 vs. 46.1 nmol/L, $P<0.001$) [54]. Similarly, in a recent large study, deficiency was lower (5%) in toddlers (1-4 years) but much higher (15.4%) in older children (5-19 years) [89]. However, in teens a large variation in deficiency has been found, being as low as (3%) (<25 nmol/L) [137] to as high as 63-68% <30 nmol/L [135]. Socioeconomic factors might explain some of the variation as it has been associated with a higher prevalence of deficiency in one study of Irish children that were largely aged over 12 years [136]. One study reported that older teens (15-18 years) had lower mean 25(OH)D and were more likely to be deficient than younger teens (13-15 years) [142]. Overall, vitamin D deficiency was more prevalent in the winter, increasing to 9% in children aged 2 years [141], 18-30% in teens [140, 143], and 26% in children aged 1-17 [136].

For levels less than <50 nmol/L, there was a similar pattern of higher prevalence in young infants and older children/adolescents. In new-born cord blood, prevalence was between 80 to 92% [121, 129, 131, 133], and with similar levels (79-92%) in preterm and term infants [121, 123, 129, 132, 133]. In young children (1-5 years), it was lower (21-39%) [89, 139, 141], affecting 36%-89% in their teens. Overall, approximately half of children aged 1-17 years had levels <50 nmol/L [54, 89, 108, 136, 142]. There was also a seasonal variation in levels <50 nmol/L with prevalence up to 85% in winter [143].

In children with fractures, more than a third (38%) had levels <50 nmol/L [144]. A greater incidence of hypo-calcaemic seizures due to vitamin D deficiency was found in males and infants [145]. In addition, it was found that girls reached a plateau of PTH concentration when 25(OH)D reaches 60 nmol/L, however this was not observed in boys [146]. One study found no correlation between antenatal vitamin D and prevalence of atopic disease at 2 and 5 years [147].

Table 1.4 Vitamin D in Children & Adolescents in Ireland

Study	n	Gender	Location	Age	Intake	25(OH)D	Season	Deficient cut off	Status (%)	<50 nmol/L	Status	Assessment Method
			(°N)	Mean (SD) (Years)	Mean (SD) (µg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
Andersen 2005 [80]	19	Female	Cork (52)	12.2 (0.8)	2.4 (1.2, 7.5) Median (2.5/97.5th)	41.3 (18.6, 59.3) Median (2.5/97.5th)	Feb/Mar 2003	<25	26	<50	89	HPLC
Hill 2006 [143]	22	Female	Cork (52)	11-13			Summer (Aug/Sept)	<25	0	<50	9	ELISA
							Winter (Feb/Mar)	<25	30	<50	85	
McCarthy 2006 [140]	17	Female	Cork (52)	12.1 (0.8)	2.6 (1.95)	39.0 (11.3)	Winter (Feb/Mar)	<25	18	<40*	47	HPLC
						64.0 (11.5)	Summer (Aug/Sept)	<25	0	<40*	6	
Hill 2008 [137]	1015		NI (54-55)		2.6	64.3 (27.3)	67% Winter	<25	3	<50	36	ELISA
						56.7 (24.3)	Winter (Nov-Mar)			<50	46	
						78.1 (27.1)	Summer (Apr-Oct)			<50	17	
	49.2%	Male		12 & 15	3	61.1 (25.1)/ 74.7 (29.7)	Winter/ Summer			<50	38	
	50.8%	Female		12 & 15	2.2	52.3 (22.6)/ 81.5 (23.9)	Winter/ Summer			<50	55	
Cashman 2008 [138]	1015		NI (54-55)		Median (Range)	Median (Range)						ELISA
	260	Male		12	1.87 (0.33-15.30)	61.1 (22.2-174.1)						
	239	Male		15	2.05 (0.44-39.52)	63.6 (5.0-165.6)						
	266	Female		12	1.49 (0.18-13.40)	59.0 (15.8-144.6)						
	250	Female		15	1.42 (0.09-16.25)	57.6 (18.8-146.8)						
Carroll 2014 [54]	252	35% Male	Dublin (53)	Range 1-17		52 (25)		<30	22	<50	55	CIA

Table 1.4 Vitamin D in Childhood and Adolescents in Ireland Continued

Study	n	Gender	Location	Age	Intake	25(OH)D	Season	Deficient cut off	Status (%)	<50 nmol/L	Status	Assessment Method
			(°N)	Mean (SD) (Years)	Mean (SD) (µg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
	Supps = 23%					37.6 (22.1)	Jan-Mar			<50	83	
						52.4 (26.8)	Apr-Jun			<50	58	
						61.5 (24)	Jul-Sept			<50	33	
						49.2 (25.4)	Oct-Dec			<50	58	
Carson 2015 [135]	1015		NI (54-55)			Median (5th, 95th)						LC/MS
	260	Boy		12		41.5 (20.3, 71.6)		<30	67			
	239	Boy		15		43.3 (18.2, 70.2)		<30	63			
	266	Girl		12		40.1 (19.8, 67.1)		<30	66			
	250	Girl		15		39.1 (15.9, 68.4)		<30	68			
Ni Chaoimh 2018 [141]	n=741	53% Male	Cork (52)	2.1	3.5 (3.1)	63.4 (20.4)		<30	5	<50	27	LC/MS
	Supp=20%					54.5 (19.9)	Winter (Nov-Apr)	<30	9	<50	45	
						71.2 (17.5)	Summer (May-Oct)	<30	1	<50	10	
McVey 2019 [139]	79	54% Male	Dublin (53)	5	1.76 (1.32)	55.0 (29.0) Median (IQR)		<30	13	<50	39	PBA
	n=43	Male			1.63 (1.4)	54.0 (36.0)		<30	9	<50	42	
	n=36	Female			1.88 (0.8)	56 (31.5)		<30	17	<50	36	
				<12		49.2 (25.4)		<30	16			
				>12		43.2 (25.4)		<30	24			
Moore 2021 [144]	116	52% Male	Dublin (53)	Range 1-16 (Mean 8.5)								
Study	**n**	**Gender**	**Location**	**Age**	**Intake**	**25(OH)D**	**Season**	**Deficient cut off**	**Status (%)**	**<50 nmol/L**	**Status**	**Assessment Method**

Table 1.4 Vitamin D in Childhood and Adolescents in Ireland Continued

Study	n	Gender	Location	Age	Intake	25(OH)D	Season	Deficient cut off	Status (%)	<50 nmol/L	Status	Assessment Method
			(°N)	Mean (SD) (Years)	Mean (SD) (µg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
	n=58 Cases					63.2 (27.4)				<50	38	LC/MS
	n=58 Controls					62.5 (21.5)				<50	29	
Glatt 2022 [108]	47	40% Male	NI (54-55)	7-11 Mean 8 (2)	6.4 (5.6)	49.17 (17.04)	Nov-Mar	<30	15	<50	55	LC/MS
Cashman 2022 [142]	246	50% Male	Ireland	13-18	3.0 (1.7-5.0)	47.8 (22.8)	Nov-Mar (57%)	<30	22	<50	55	LC/MS
Scully 2022 [136]	1269	69% Female	Dublin (53)	Range 1-17 (Mean 15)		43.8 (25.5) GM Mean (SD)	44% Winter (Oct-Feb)	<30	23	<50	51	LC/MS
McKenna 2022 [89]	215	60% Male	Dublin (53)	Infants	<1			<30	6		15	PBA
	538	53% Male		Toddlers	1-<5				5		22	
	5524	41% Male		Children/ Adolescents	5-20				15		48	

ELISA; enzyme-linked immunosorbent assay, LC-MS/MS; Liquid Chromatography with tandem mass spectrometry, PBA; Protein Binding Assay, RIA; Radioimmunoassay, IQR; Interquartile Range. °N; Northern Latitude (Degrees). *Alternative cut-off value.

- **Adults (<50 years) (n=17)**

Vitamin D deficiency was prevalent in Irish adults (<50 years) and ranged from 7% to 38% [84, 148], though was higher in younger adults and in winter (Table 1.5). The largest study (n=63,290) revealed that 13% were deficient between 2020-2021 [89]. In Dublin (53°N), between 25-30% were deficient [16, 149], though there was a lower prevalence of 10-11% (<25 nmol/L) at a similar latitude in the West of Ireland [150]. In Coleraine (55°N, Northern Ireland) there was a wide variation in deficiency (2-23%), though sample sizes were small (n<100) [98, 151, 152]. In two studies, deficiency was 0-2%, though these also had small (n<100) sample sizes [98, 143].

Levels <50 nmol/L were found in more than half of adults living in Dublin [16, 149], 44% in those living in the West [150] and between (14-72%) in Coleraine [98, 151, 152]. In several locations across Ireland, a similar prevalence of between 40-55% was identified [84, 99]. In younger adults (age 18-39) nearly half (45%) having levels <50 nmol/L [153, 154] and up to 58% <50 nmol/L in winter [25, 143, 154, 155], with this proportion being higher in Cork [143] and Dublin [25, 154, 155].

Despite not generally being considered an 'at-risk' group, studies in Ireland indicate that deficiency is more prevalent in younger versus older adults [25, 89, 148, 149, 154-156]. For example, 18% of younger adults (age 18-39) versus 15% aged (40-49) were deficient [153, 154]. In addition, urban dwelling younger adults had higher levels of deficiency (<25 nmol/L) than rural ones [156]. In general, Irish females had higher 25(OH)D than males [25, 89, 150, 153, 154, 156] except in one study, where older women had more deficiency (<25 nmol/L) [143]. Males were reported to be up 32% more likely to be deficient in one large study [154].

Table 1.5 Vitamin D Status in Adults in Ireland

Study	n	Sex	Location	Age	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
			(°N)	(Years)	(μg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
Hill 2006 [143]	23	Female	Cork (52)	23-50			Summer (Aug/Sept)	<25	0	<50	4	ELISA
							Winter (Feb/Mar)	<25	0	<50	35	
	51	Male	Cork (52)	20-64			Summer (Aug/Sept)	<25	0	<50	7	
							Winter (Feb/Mar)	<25	0	<50	33	
O'Sullivan 2008 [155]	70	40% Male	Dublin (53)	36.34 (9.53) Mean (SD)				<25	13	<50	51	RIA
							Summer*	<25	10	<50	46	
							Winter*	<25	17		58	
Muldowney 2011 [157]	37	35% Male	Ireland (51-55)	33 (27-37) Mean (Range)	2.6 (1.3–5.1) Median (IQR)	52.9 (35.3–68.6) Median (IQR)	Jan-March			<50	43	ELISA
Cashman 2013 [84]	1,132	50% Male	Ireland (51-55)	18-84 (Range)	5.2	60.0 (58.6, 61.4) Mean (95% CI)		<30	7	<50	40	ELISA
Magee 2013 [99]	84	89% Male	Ireland (51-55)	25 (22, 30) Median (25^{th}, 75^{th})	4.4 (2.5,7.6) Median (25, 75^{th})	48.4 (32.6, 64.0) Median (25^{th}, 75^{th})				<50	55	ELISA
Kilbane 2014 [149]	10,181	n/a	Dublin (53)			54.4 (31.1–81.7) Median (IQR)		<30	29	<50	51	PBA
	1,813			<20		57.7 (35.9)						
	6,609			20-70		59.7 (39.5)						
	1,759			>70		62.1 (51.5)						
McKenna 2015 [16]	43782 samples	32% Male	Dublin (53)	49.8 (25.6)		54.6 (31.4)		<30	25	<50	50	LC/MS

Table 1.5 Vitamin D Status in Adults in Ireland Continued

Study	n	Sex	Location	Age	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
			(°N)	(Years)	(μg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
Todd 2016 [151]	22	45% Male	Coleraine (55)	>18 (Mean 25.2)	6.3 (6.2)	59.8 (29.9)	Oct-Mar	<30	23	<50	41	LC/MS
Laird 2017 [25]	5,287		Dublin (53)	48.7 (16.4)								
		29% Male				53.9 (31.0)	Winter (Oct-Feb)	<30	15	<50	39	LC/MS
		27% Male					Summer (Mar-Sept)	<30	11	<50	32	
Todd 2016 [98]	92	50% Male	Coleraine (55)	25(5)		76.5 (27.0)	Feb-Nov	<30	2	<50	14	LC/MS
Delos Reyes 2017 [150]	15,708 samples	27% Male	Galway (53)	52.6 (16.5)		54 (35-74) Median (IQR)	36.3% Winter (Dec-Feb)	<25	11	<50	44	LC/MS
Todd 2017₇ [152]	42	43% Male	Coleraine (55)	20 (2) Mean (SD)	Mean (SD)	Mean (SD)	Nov-Apr	<30	22	<50	72	LC/MS
	22 vitamin D				6.7 (5.3)	47.4 (13.3)						
	20 Placebo				4.9 (2.5)	43.1 (22.0)						
Griffin 2020 [156]				Range (Mean)		Median (min-max)						
Urban	1,448	25% Male	Galway (53)	18-39 (31.5)		45.7 (13-264)		<25	19	<50	56	LC/MS
	758	26% Male		40-49 (44.9)		47.1(13-296)		<25	15	<50	54	
Rural	3,006	26% Male		18-39 (31.6)		46.3 (13-300)		<25	16	<50	55	
	2,496	31% Male		40-49 (44.9)		46.8 (13-288)		<25	14	<50	56	
Griffin 2020 [153]	24,302 samples		Galway (53)	Mean (SD)		Median (Min-max)		<25	17	<50	36	LC/MS
	Community 15,319	28% Male		52.0 (16.4)		50.3 (13-300)		<25	13	<50	49	
	Outpatient 6,371	32% Male		54.4 (17.9)		47.5 (13.0- 288.0)		<25	17	<50	53	
	Inpatient 2,339	39% Male		70.2 (17.5)		33.6 (13-264)		<25	37	<50	68	

Table 1.5 Vitamin D Status in Adults in Ireland Continued

Study	n	Sex	Location	Age		25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
			(°N)	(Years)	(μg/day)	(nmol/L) Mean (SD)		(nmol/L)	(%)	(nmol/L)	(%)	
	Nursing Home 273	36% Male		81.5 (11.7)		29.7 (13-147.8)		<25	42	<50	67	
Griffin 2020 [153]	5,842		Galway (53)	18-39		45.3 (13-300) Median (Min-max)		<25	18	<50	56	LC/MS
	4,231			40-49		46.2 (13-296) Median (Min-max)		<25	15	<50	56	
Scully 2020 [154]	36,466	28% Male	Dublin (53)	50.7 (18-109) Mean (Range)		52.8 (30.8) GM Mean (SD)		<30	15	<50	38	LC/MS
						46.8 (30.3) GM Mean (SD)	Winter (Dec-Feb)	<30	23	<50	49	
						58.6 (30.5) GM Mean (SD)	Summer (Jun-Aug)	<30	8	<50	24	
Scully 2020 [154]	18,941	28% Male	Dublin (53)	18-49		48.8 (29.8)	All year	<30	18	<50	45	
McKenna 2022 [89]	63,290	32% Male	Dublin (53)	20-<65			All year	<30	13	<50	43	PBA

ELISA; enzyme-linked immunosorbent assay, LC-MS/MS; Liquid Chromatography with tandem mass spectrometry, PBA; Protein Binding Assay, RIA; Radioimmunoassay, IQR; Interquartile Range. °N; Northern Latitude (Degrees). *Alternative cut-off value

- **Older Adults (n=23)**

Vitamin D deficiency is prevalent in older Irish adults (>50 years) and in large studies ranged between 8-32% [78, 158] (Table 1.6). Though in small studies (n<100), prevalence was as low as 0-7% and as high as 35-86% in others [143, 159-162]. However, in the nationally representative study, The Irish LongituDinal Study on Ageing (TILDA) of 5,356 older adults, 13% were deficient, similar to the findings of an EU meta-analysis [40, 163]. In the large Trinity, Ulster, Department of Agriculture cohort (TUDA) study, prevalence of deficiency ranged from 13.8-27.3% in older unsupplemented adults, and up to 43.6% in those who were frail and cognitively impaired [46]. However, participants were hospital outpatients and not representative of the wider population.

Despite the small variation in latitude in Ireland, a North-South gradient has been identified in older adults [48]. Regional variation was also found in the TILDA study with a lower prevalence of deficiency in Leinster compared to other provinces likely reflecting in part variances in UVB exposure [48]. However, prevalence rates have also varied within the same areas with deficiency reported between 11-86% in Dublin [154, 159], 2-17% in Cork, [143] 10-42% in Galway and 14-35% in Northern Ireland [40, 162]. Socioeconomic factors may play a role as suggested by the TILDA study and one large investigation in the Dublin and surrounding areas [153, 164]. Urban residing older adults had increased rates of deficiency [156]. Compared to community dwelling older adults, nursing home residents were also at higher risk [156], with 35-42% deficient in both the Republic and Northern Ireland [153, 162]. Hospital in-patients also had lower vitamin D status than those in primary care [89].

Between 30-75% of Irish adults (>50 years) were found to have levels less than 50 nmol/L [46, 165, 166], with this more prevalent in those living in northern locations and urban areas [48, 156]. Predictors of vitamin D status in older adults include smoking, supplement use and sun holiday travel, BMI, physical frailty, and lower asset wealth, with supplementation being the strongest determinant [46, 48].

Vitamin D deficiency was also more prevalent during winter in older Irish adults [48, 140, 143, 160]. Seasonal decline in status was greater with increasing age with levels <50 nmol/L in winter occurring in 64% (aged 70-75) versus 34% (aged 51-69) [143]. This was replicated by the TILDA study which found 43% <50 nmol/L, with higher rates in the winter and in those aged 70+ compared with 50+ [48, 158]. Despite a reduced capacity for dermal synthesis, UVB light and sun enjoyment were still identified as an important contributor to vitamin D status in older Irish adults [78].

Vitamin D deficiency has been associated with several health outcomes in older adults including increased risk of prediabetes [167], depression, emergency department attendance and hospitalisation [168, 169]. It was associated with an increased COVID mortality risk, particularly in those over 70 years [148]. In another study, an increased risk of Orthostatic Hypotension (OH) with low vitamin D status was found [170], but this was not replicated in a later, larger analysis [166].

Table 1.6 Vitamin D Status in Older Adults in Ireland

Study	n	Gender	Location	Age	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status (%)	Assessment Method
			(°N)	Mean (SD) (Years)	Mean (SD) (μg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
Freaney 1993 [159]	29	48% Male	Dublin (53)	74 (65-87) Mean (Range)		13 (12)	Jan-Mar	<25	86			PBA
Hill 2005 [160]	59	Female	Cork (52)	51-69	3.2 (2.0)	54.5 (27.8)	Feb/Mar 2002	<25	7	<50	53	ELISA
	48					75.4 (29.6)	Aug/Sept 2002	<25	0	<50	17	
	47					68.6 (34.9)	Feb/Mar 2003	<25	2	<50	36	
Andersen 2005 [80]	43	Female	Cork (52)	72.3 (1.5)	4.0 (1.4, 13.1) Median (2.5^{th}/97.5^{th})	43.7 (17.0, 89.1) Median (2.5^{th}/97.5^{th})	Feb/Mar 2003	<25	14	<50	60	HPLC
McCarthy 2006 [140]	43	Female	Cork (52)	72.4 (2.2)	4.6 (9.34)	47.3 (21.1)	Winter (Feb/Mar)	<25	14	<40*	37	HPLC
						59.7 (20.0)	Summer (Aug/Sept)	<25	2	<50	19	
Hill 2006 [143]	44	Female	Cork (52)	51-69			Summer (Aug/Sept)	<25	0	<50	16	ELISA
							Winter (Feb/Mar)	<25	2	<50	34	
	31			70-75			Summer (Aug/Sept)	<25	0	<50	19	
							Winter (Feb/Mar)	<25	17	<50	64	
DeLappe 2006 [165]	114	Female	Galway (53)	79.7 (9.6)		35.8 (23.3)		<20	25	<50	75	RIA
Hill 2006 [161]	95	Female	Cork (52)	64.1 (51.0-75.6) Mean (Range)	2.97 (1.86)	57.2 (26.9)	Feb/Mar	<25	7	<50	48	ELISA
Lardner 2011 [164]	143	Female	Galway (53)	61 (40-85) Mean (Range)			26% Winter (Nov-Mar)	<25	10	<50	47	RIA

Table 1.6 Vitamin D Status in Older Adults in Ireland Continued

Study	n	Gender	Location	Age	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status (%)	Assessment Method
			(°N)	Mean (SD) (Years)	Mean (SD) (μg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
Laird 2014 [40]	957	50% Male	Northern Ireland (55)	70.5 (65.9-74.9) Median (IQR)		43.9 (29.3-62.2) Median (IQR)		<25	14	<75*	82	LC/MS
Osuafor 2016 [171]	76	68% Female	Dublin (53)	83 (81-85)		Mean (CI)		<30	30	<50	49	LC/MS
	52	Female				61.4 (50.7-72.2)						
	24	Male				51.7 (35.8-67.6)						
Laird 2017 [48]	5,356	53% Female	Ireland (51-55)	62.9 (50-98) Mean (Range)		51.3 (50.5-52.1) GM Mean (95%CI)		<30	13	<50	43	LC/MS
Laird 2017 [48]						44.1 (43.0-45.2) GM Mean (95%CI)	Winter (Dec-May)	<30	24	<50	59	
O'Sullivan 2017 [78]	5138	67% Female	Ireland (51-55)	73 (Median)		54.5 (34-81) Median (IQR)	20% Winter*	<40*	32	≥40*	68	LC/MS
Griffin 2019 [156]			Galway (53)	Range (mean)		Median (range)						
Urban	866	26% Male		50-59 (55.1)		55.0 (13-274)		<25	10	<50	43	
	831	26% Male		60-69 (64.8)		60.2 (13-239)		<25	11	<50	37	
	574	26% Male		70-79 (74.5)		59.6 (13-173)		<25	12	<50	37	
	310	26% Male		80-89 (84.0)		49.3 (13-161)		<25	20	<50	50	
	37	14% Male		>90 (93.1)		36.0 (13-137)		<25	35	<50	62	
Rural	2393	34% Male		50-59 (55.0)		49.9 (13-194)		<25	12	<50	51	
	2207	37% Male		60-69 (64.8)		53.0 (13-279		<25	13	<50	46	
	1499	39% Male		70-79 (74.6)		47.8 (13-221)		<25	20	<50	52	

Table 1.6 Vitamin D Status in Older Adults in Ireland Continued

Study	n	Gender	Location	Age	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status (%)	Assessment Method
			(°N)	Mean (SD) (Years)	Mean (SD) (μg/day)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
	949	35% Male		80-89 (82.3)		35.7 (13-182)		<25	34	<50	62	
	216	25% Male		>90 (92.9)		32.0 (13-148)		<25	40	<50	69	
				Range		Median (range)						
Griffin 2020 [153]	4447		Galway (53)	50-59		50.5 (13-194)		<25	12	<50	49	LC/MS
	4410			60-69		53.6 (13-279)		<25	13	<50	45	
	3132			70-79		50.3 (13-221)		<25	19	<50	50	
	1884			80-89		39.2(13-184)		<25	31	<50	60	
	356			>90		31.1 (13-184)		<25	42	<50	69	
Laird & Kenny 2020 [158]	5,382		Ireland (51-55)	55+			Winter (Dec-May)	<30	21	<50	33	LC/MS
	(Tilda wave 1)			70+			Winter (Dec-May)	<30	27	<50	30	
				55+			Summer (Jun-Nov)	<30	8	<50	27	
				70+			Summer (Jun-Nov)	<30	12	<50	32	
Scully 2020 [154]	17,525	28% Male	Dublin (53)	50-109 (Range)	59.7 (30.8) GM Mean (SD)		All year	<30	11	<50	30	LC/MS
Feehan 2022 [162]	87	40% Male	Northern Ireland (55)	83.2 (7.9)		49.5 (35.6)	May-Mar	<25	35	<50	52	LC/MS
McKenna 2022 [89]	30,908	37% Male	Dublin (53)	>65			All year	<30	12	<50	38	PBA
Barrett 2022 [148]	232	60% Male	Dublin (53)	56 (17-99) Median (Range)			All year	<30	38	<50	64	ECLIA

ELISA; enzyme-linked immunosorbent assay, LC-MS/MS; Liquid Chromatography with tandem mass spectrometry, PBA; Protein Binding Assay, RIA; Radioimmunoassay, ECLIA; Electrochemiluminescence immunoassay. °N; Northern Latitude (Degrees). *Alternative cut-off value

- **At-Risk Populations / Medical Conditions (n=28)**

Ethnic Populations

The largest and only study to focus on an ethnic population discovered that more than two thirds of Southeast Asians were vitamin D deficient, but only included 186 patients who lived in the Dublin area [51] (Table 1.7). There were only three other studies that reported vitamin D status in those of non-Caucasian ethnicity, with small sample sizes and the largest only having 81 adults [52-54]. Non-Caucasian pregnant women had greater deficiency (59-88%) compared to Caucasians (36%) [52], while another study identified a 19 nmol/L difference in mean 25(OH)D between Caucasian and non-Caucasian pregnant women [53]. Mean 25(OH)D was also lowest in children of African ethnicity living in Ireland [54]. Ethnic minorities living in northern locations are known to be at increased risk of low vitamin D status due to reduced efficiency of cutaneous synthesis [50, 172].

Medical Conditions

Malabsorption Disorders

There were five studies of adults with Crohns disease (CD) [71, 173-176] though sample sizes were (<100). Prevalence of levels <50 nmol/L were 50-64% [71, 173, 175] in keeping with a global meta-analysis where half had levels <50 nmol/L [177]. A strong seasonal effect was also found, with about 20% having levels <50 nmol/L post-summer versus 50% post-winter [174, 176] and with up to 90% with levels <80 nmol/L [71]. Furthermore, wintertime levels <50 nmol/L were twice as common (50%) compared to healthy controls (25%) [174]. In a double blind RCT, CD patients supplemented with 2000 IU/day had lower deficiency rates (15% versus 50%), reduced inflammatory markers and improved quality of life scores [175]. Crohn's patients in Ireland who had bowel surgery were also three times more likely to have levels <50 nmol/L compared to non-Caucasians [178]. The vast majority (88%) of Irish patients with refractory coeliac disease had levels <50 nmol/L (88%), as did those with a recent diagnosis (58%) compared to patients with controlled disease [179].

Other Disorders

In Irish patients with Multiple Sclerosis (MS), significantly greater deficiency (<25 nmol/L) was found compared to age/sex matched controls (28.3% vs. 19.2%) [180]. Mean 25(OH)D levels were also higher in areas with a lower prevalence of MS [180]. An RCT found that supplements did not improve markers of immune function in patients with clinically isolated syndrome CIS (a precursor of MS) [181]. However, a very small study (n=4) found supplementation of 5000-1000 IU/day improved inflammatory markers [182]. Nearly two third (65%) of patients with Systemic Lupus Erythematosus (SLE) had levels <75 nmol/L after the summer [183]. In psoriasis patients, 75% were found to have

wintertime levels <50 nmol/L [184]. and following UVB exposure 25(OH)D increased and symptoms cleared [184]. Additionally, in patients attending a rheumatology clinic, 26% were vitamin D deficient (<25 nmol/L), and 70% had levels <53 nmol/L [185] while a deficiency prevalence of 41% was found in patients with Total Knee Arthroplasty (41%) [186]. An increased prevalence of hyperparathyroidism was found in Irish Travellers (n=5) with Mucolipidosis type II who had vitamin D levels below 50 nmol/L [187].

In adults with Chronic obstructive pulmonary disease (COPD), vitamin D status was low (<50 nmol/L) in 47%, particularly in winter (75%) and in house-bound patients [188]. In patients with Obstructive Sleep Apnea (OSA), 72-89%, had levels <50 nmol/L, and 98% <75 nmol/L [189, 190]. Prevalence of levels <50 nmol/L was also high in renal patients (69%) [191] and those who had thyroidectomy (75%) [192]. Between 35-50% of Irish asthmatic children had vitamin D levels <50 nmol/L [193, 194], in keeping with a recent global meta-analysis [195]. Up to 40% of children with autism had levels <50 nmol/L and 75% <75 nmol/L [193, 196].

Table 1.7 Vitamin D Status in At-Risk Populations in Ireland

Study	n	Population	Supp Users	Location	Age	Gender	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
			(%)	(°N)	Mean (SD)		Mean (SD)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
Keavney 1996 [179]	43	Coeliac		Dublin (53)	Mean (range)			Mean (SE)	NA					ELISA
	19	Newly diagnosed	21		52 (28-80)	16% Male		63.3 (11.3)				<50	58	
	16	Treated	0		46 (28-66)	25% Male		68.3 (7)					25	
	8	Refractory	37.5		45.6 (26-67)	0% Male		28.5 (6)					88	
McCarthy 2005 [174]	44	Crohns Disease	32	Cork (52)	36.9 (11.1)		6.7 (5.1)	75 (27.8)	Late-summer (Sept-Oct)	<50	18	<80*	61	ELISA
			44					80.1 (43.6)	Late-Winter (Mar)	<50	50	<80*	84	
	44	Controls	30		36.7 (11)		6.7 (4.8)	105.3 (55.5)	Late-summer (Sept-Oct)	<50	5	<80*	32	
			38					56.6 (22.1)	Late-Winter (Mar)	<50	25	<80*	56	
Gilman 2006 [176]	58	Crohns Disease	36	Cork (52)	38.1 (10.9)	40% Male	7.1 (5.4)	73.9 (28.0)	Late-summer (Sept-Oct)	<50	19			ELISA
								56.9 (23.7)	Late-winter (Mar)	<50	50			
Lynch 2007 [197]	59	Renal Transplant		Dublin (53)	46.2 (12.6)	58% Male	Median (IQR)							
	34	Male	6				4.7 (2.2-6.8)			<10 μg	91			FFQ
	25	Female	16				4.2 (2.4-5.8)			<10 μg	87			
Cusack 2008 [183]	52	Lupus	40	Dublin (53)	43 (Median)	10% Male		63.03 (23.3)	Jul-Sept	<25	4	<75*	65	RIA

Table 1.7 Vitamin D Status in At-Risk Populations in Ireland Continued

Study	n	Population	Supp Users	Location	Age	Gender	Intake	25(OH)D	Season	Deficient cut off	Status	<50 nmol/L	Status	Assessment Method
			(%)	(°N)	Mean (SD)		Mean (SD)	(nmol/L) Mean (SD)		(nmol/L)	(%)	(nmol/L)	(%)	
Lonergan 2011 [180]	632	MS		Donegal (55), Wexford (52), Dublin (53)	48 (Mean)	33% Male		38.57 (13.3-161.9) Mean (range)		<25	28			RIA
Haroon 2011 [185]	231	Rheumatology		Cork (52)	53 (16)	45% Male			Jan-Jun	<25	26	<53*	70	CIA
Nic Suibhne 2012 [71]	151	81 CD	43	Dublin (53)	36.4 (11.0)	40% Male		47.8 (27.3)	69% Winter (Oct-Mar)	<50	63	<80*	90	RIA
Nic Suibhne 2012 [71]		70 Controls	16		36.3 (9.5)	40% Male		51.8 (24.5)	44% Winter (Oct-Mar)	<50	55			
McCarroll 2012 [170]	38	Orthostatic Hypotension		Dublin (53)	79.0 (6.8)	37% Male		40.5 (22.2)	Jan/Feb					CIA
	38	Healthy Controls			78.2 (5.8)	37% Male		61.1 (23.1)						
Kelly 2011 [173]	75	Crohns Disease	44	Dublin (53)	36.3 (1.3)	39% Male				<50	64			RIA
Griffin 2014 [192]	121	Thyroidectomy		Cork (52)	51.6 (14-87) Mean (range)	10% Male		39.5 (10-120) Mean (IQR)	Nov 09-Sept 12	<25	31	<50	75	CIA
Raftery 2015 [175]	27	Crohns Disease		Dublin (53)	Mean (SD)			Mean (SD)						
	14	Placebo			36.7 (12.1)	43% Male		51.8 (20.7)	Oct-Dec	<50	50	<75*	79	LC/MS
	13	Treatment			36.5 (11.8)	54% Male		69.2 (7.0)	Oct-Dec	<50	15	<75*	54	
					Mean			Non-supp/ Supp		<30		<50		
McCarroll 2015 [46]	1895	Hypertensive		NI (54-55)	70.1			45.6 (23.5)/ 67.0 (27.1)			27.3/ 6.4		66.0/ 33.2	LC/MS

Table 1.7 Vitamin D Status in At-Risk Populations in Ireland Continued

			(%)	(°N)	Mean (SD)		Mean (SD)	Mean (SD) (nmol/L)		(nmol/L)	(%)	(nmol/L)	(%)	
	1233	Bone		Dublin (53)	71			60.6 (32.1)/ 82.5 (26.8)			13.8/ 3.0		43.4/ 10.5	
	1316	Cognitive		Dublin (53)	80.4			38.2 (22.9)/ 73.6 (29.5)			43.6/ 6.5		75.0/ 22.9	
Kerley 2016 (190)	106	Obstructive Sleep Apnea (OSA)	N/a	Dublin (53)	54.5 (Median)	73% Male				<50	72	<75*	98	CIA
Kerley 2016 (194)	44	Asthma		Dublin (53)	8.7 (Mean)	52% Male		51 (24–80) Mean (range)	Nov-Jan	<50	50			LC/MS
Kerley 2017 (189)	19	Obstructive Sleep Apnea (OSA)	N/a	Dublin (53)	55 (Mean)	75% Male		37.2 (14.5-86.5) Mean (range)	Nov-Jan	<50	89			CIA
Kerley 2017 (196)	42	Autism	N/a	Dublin (53)	7.1 (Mean)	90% Male		54.2 (19.7)	Sept-Dec	<50	40			LC/MS
O'Connell 2017 (181)	29	CIS (Pre-MS)	n/a	Dublin (53)	18-55 (Range)	34% Male		53 (Mean)						LC/MS
Kelly 2017 (186)	79	Total Knee Arthroplasty	41	Galway (53)	68.2	39% Male		59.1 (22.6)	NA	<50	41	<75*	75	(N/A)
	85	Control	21		61.3	52% Male		62.0 (22.9)		<50	26	<75	77	
Carson 2018 (188)	51	COPD		Belfast (54-55)	68.7 (7.2)	55% Male		33.7 (28.4)	End of winter (Mar/Apr)	<50	75			LC/MS
Carson 2018 (188)								52.5 (30.5)	End of summer (Sept/Oct)	<50	47			
Lynch Cronin 2019 (191)	18	Renal transplant recipients	N/a	Cork (52)	53 (13)	72% Male		39.7 (14.9)	Oct-May	<50	69	50-75	31	EIA
Kerley 2020 (193)	17	Asthma	N/a	Dublin (53)	9 (4)	65% Male		57 (19)	Sept-Apr	<50	35	<75*	47	LC/MS
	18	Autism	N/a		8 (3)	83% Male		58 (18)	Sept-Apr	<50	11	<75*	71	

Table 1.7 Vitamin D Status in At-Risk Populations in Ireland Continued

			(%)	**(°N)**	**Mean (SD)**		**Mean (SD)**	**Mean (SD) (nmol/L)**		**(nmol/L)**	**(%)**	**(nmol/L)**	**(%)**	
Laird 2020 [51]	186	Southeast Asians	N/a	Dublin (53)	32 (Median)	51% Male		median (25^{th}, 75^{th})	Winter (Dec-Feb) 44% M/20% F	<30	67	<50	93	LC/MS
						Male		18.0 (27.0, 36.0)						
						Female		25.0 (17.0, 30.0)						

CIS; Clinically Isolated Syndrome, COPD; Chronic Obstructive Pulmonary Disease, MS; Multiple Sclerosis, ELISA; enzyme-linked immunosorbent assay, LC-MS/MS; Liquid Chromatography with tandem mass spectrometry, PBA; Protein Binding Assay, RIA; Radioimmunoassay, IQR; Interquartile Range, Non-supp; Non-supplemented population, Supp; Supplemented population, °N; Northern Latitude (Degrees).
*Alternative cut-off value

1.3.2 Dietary Vitamin D Intake (n=23)

- **Children & Adolescents**

There were 7 studies that identified dietary vitamin D intake in Ireland, with a mean (SD) between 2.2(2.2) μg/day to 4.4 (3.1) μg/day (Table 1.8). For children aged 1-5 years, 5 μg/day intake is recommended, with guidelines for older children (6-11 years) recently increased to 10 μg/day [2, 4]. However, the latest nationally representative dietary surveys indicate that children fall far short of meeting these, with the majority (70-84%) of younger (1-4 years) and older (5-18 years) children (94%) not meeting adequate intake levels [85, 86, 96]. In small study of 5-year-olds, just 6.2% had intakes above 5 μg/day, and 37.5% had levels <50 nmol/L [139]. The first National Children's Food survey (2003/2004) of 5-12 years olds calculated the mean (SD) of dietary vitamin D as 2.3 (2.3) μg/day [198], with the majority (98-99%) having intakes less than 10 μg/day [100, 198]. When repeated a decade later, 94% of children had inadequate vitamin D intakes (<10 μg/day) [86, 97]. The National Teen Food Survey (2005/2006) found adolescents (aged 13-17) had a mean (SD) dietary intake of 2.7 (2.4) μg/day [199]. Its recent follow up has found that while intake has increased (mean (SD) 3.7 (3.0)), most teens have inadequate dietary intakes (94% <10 μg/day) [200].

In children aged 1-4, milk/formula represents the largest dietary contribution of vitamin D, followed by meat and yoghurt [96]. In children (age 5-12 years) it is fortified cereals, followed closely by meat and milk/yoghurt [86]. Despite its low content, meat is the overall largest source of vitamin D for teens (age 13-18 years), followed by fortified cereal and eggs [85]. As a result of the low vitamin D content of commonly consumed foods, meeting the recommended levels through diet alone is difficult and may be inadequate to maintain wintertime sufficiency. A modelling study estimates that children in northern locations (40-63°N) require 33.8 μg/day to maintain serum >50 nmol/L [201].

- **Adults**

We identified 10 studies that identified dietary vitamin D intake in Irish adults, with a mean (SD) intake between 3.0 μg/day (2.5) and 6.9 μg/day (10.5). The first dietary survey in 1997/1999 indicated Irish adults had inadequate mean intakes of vitamin D (3.4 μg/day) [202, 203], with 74% of 18-64 year olds having intakes less than 5 μg/day [204] and 93% less than 10 μg/day [205]. Lowest intakes were identified in younger adults (18-35 years) (mean 2.8 μg) compared to those aged 36-50 (mean 3.4 μg) or 51-64 years (mean 5.8 μg) [202]. Disadvantaged women were less likely to have adequate vitamin D intake than non-disadvantaged [107]. In 2011, the National Adult Nutrition Survey (NANS) found no improvement, with 90% of adults aged 18-64 having intakes less than 10

μg/day, compared to 87% of men and 77% of women over 65 years [94]. Measured vitamin D2 values were detected in 80% of NANS participants, indicating its contribution to nutritional adequacy [206]. Pregnant women also had inadequate intakes (1.9-3.2 μg/day) with 80-99% not meeting the recommendations [207-209].

- **Effect of Vitamin D Food Fortification**

Currently, fortified foods provide 11% of total dietary vitamin D intake in adults and have the potential to reduce inadequacy in Irish adults [210]. In Irish children aged 1-4 years, fortifying cow's milk and a 5 μg/day supplement in modelling studies were estimated to reduce inadequate intakes (<10 μg/day) from 95% to 12-36% [211]. However, this though would be insufficient for meeting the EFSA adequate intake level (15 μg/day) [212]. In older adults, an association has been also found between fortified milk and better vitamin D status [46] Fortification of food staples such as milk and bio-enriched eggs was also estimated to attenuate the wintertime reduction in vitamin D status in Irish adults [213, 214]. In one modelling study, fortification of numerous food items was required to ensure vitamin D adequacy (>50 nmol/L) all year around in Irish adults [215]. In particular, fortification of milk and bread was reported as having the potential to ensure that 70% of older Irish adults (>50 years) meet a daily allowance of 10 μg/day [216]. A more novel way using 'biofortification of food' with vitamin D via feed modification and UV radiation in Ireland has also shown potential, particularly enriched meat, and should be further explored [217]. In 2003, mandatory fortification of butter/spreads and milk products in Finland enabled 91% of the population to reach sufficiency by 2011 [218], so public health measures like this that increase fortified food consumption should be considered in Ireland.

Table 1.8 Vitamin D Status and Intake in Dietary Studies in Ireland

Study	n	Supp Users	Sex	Location	Age	Intake	25(OH)D	Season	Status	Assessment Method
				(°N)	(Years)	Mean (SD) (μg/day)	Mean (SD) (nmol/L)		(%)	
O'Brien 2001 [202, 203]	1379		48% Male	Ireland (51-55)	18-64	3.7 (3.4)	3.7 (8.7)			7-Day weighed Food Diary
					18-35	3.0 (2.5)	2.8 (3.1)			
					36-50	3.9 (3.2)	3.4 (3.3)			
					51-64	4.4 (4.5)	5.8 (17.2)			
IUNA (NCFS) 2003/04 [198]	594		49% Male	Ireland (51-55)	5-12	2.3 (2.3)				7-Day weighed Food Diary
	293 Male					2.2 (2.2)				
	301 Female					2.3 (2.3)				
Hill 2004 [204]	1379		48% Male	Ireland (51-55)	18-64	4.2			74% <5 μg	7-Day weighed Food Diary
						4.6		Winter (Oct-Mar)		
						4.1		Summer (Apr-Sept)		
IUNA (NTFS) 2005/06 [199]	441		51% Male	Ireland (51-55)	13-17	2.7 (2.4)				7-Day weighed Food Diary
	224-Male					3.0 (2.6)				
	217-Female					2.3 (2.2)				
IUNA (NPSNS) 2011 [96]	500		50% Male	Ireland (51-55)	12-59mo	3.3 (3.8)			70-84% <5 μg	4-Day Food Diary
IUNA (NANS) 2011 [94]	1274		50% Male	Ireland (51-55)	18-64	4.3 (6.2)		54% Winter (Sept-Feb)	90%<10 μg	4-Day Food Diary
	226		47% Male		>65	6.9 (10.5)			87%m/77%w <10 μg	

Table 1.8 Vitamin D Status and Intake in Dietary Studies in Ireland Continued

Study	n	Supp Users	Sex	Location	Age	Intake	25(OH)D	Season	Status	Assessment Method
				(°N)	(Years)	Mean (SD) (μg/day)	Mean (SD) (nmol/L)		(%)	
McGowan 2011 [207]	64	(excluded)	Female (Pregnant)	Dublin (53)	31.6 (4.1)	Median (IQR)			80% <10 μg	3-Day Food Diary
					Trimester 1	2 (1.2-2.9)				
					Trimester 2	1.9 (1.3-3.6)				
					Trimester 3	2.1 (1.1-3.6)				
McGowan & McAuliffe 2012 [209]	248		Female (Pregnant)	Dublin (53)	32.6 (4.0)	2.7 (2.1)		Mar 09-Jan 11	99% <10 μg	3-Day Food Diary
Cashman 2013 [84]	1500 NANS 2011	17.5	50% Male	Ireland (51-55)	18-84	5.2 (Mean)	Mean (95% CI)			4-Day Food Diary
	1132 with 25(OH)D						60·0 (58.6, 61.4)	All year		ELISA
							53·1 (51.2, 55.1)	Winter (Nov-Mar)		
							65·5 (63.6, 67.4)	Summer (Apr-Sept)		
Black 2014 [100]	296-2004 Children's Survey	21	49% Male	Ireland (51-55)	5-8	2.8 (2.4)			98% <10 μg	7-Day weighed Food Diary
	298-2004 Children's Survey	16	50% Male	Ireland (51-55)	9-12	2.8 (2.1)			99% <10 μg	7-Day weighed Food Diary
	441-2007 Teens Survey	15	52% Male	Ireland (51-55)	13-17	3.2 (2.5)			98% <10 μg	7-Day weighed Food Diary
Black 2014 [205]	1379-1999 Survey	17		Ireland (51-55)	18-64	4.3 (4.0)			93% <10 μg	7-Day weighed Food Diary
	1274-2009 Survey	16		Ireland (51-55)	18-64	5.0 (6.4)			90% <10 μg	4-Day Food Diary
Lindsay 2014 [219]	52	40	Female (Pregnant)	Dublin (53)	32 (6.3)	5.1 (6.5)		May-Sept	90% <10 μg	24hour recall
Lindsay 2015 [208]	75		Female (Pregnant)	Dublin (53)	31 (4.5)	3.2 (2.5)		Mar-Nov	90% <10 μg	3-Day Food Diary

Table 1.8 Vitamin D Status and Intake in Dietary Studies in Ireland Continued

Study	n	Supp Users	Sex	Location		Intake	25(OH)D	Season	Status	Assessment Method
				(°N)	(Years)	Mean (SD) (μg/day)	Mean (SD) (nmol/L)		(%)	
Hennessy 2017 [220]	500-NPNS 2012	17	50% Male	Ireland (51-55)	1-4	3.5 (3.7)			93%<10 μg / 78%<5 μg	4-day Food Diary
IUNA (NCFS II) 2017/18 [86]	600	10	50% Male	Ireland (51-55)	5-12	4.2 (3.1)			94% <10 μg	4-Day Food Diary
	300 Male					4.4 (3.1)				
	300 Female					4.1 (3.0)				
McVey 2018 [139]	97		47% Male	Dublin (53)	5.09	1.83 (1.64) Median (IQR)	Median (IQR)	All year	6.2% >5 μg	FFQ
	32 w/ 25(OH)D		62.5% Male	Dublin (53)	5.09		52.25 (24.7)	n/a	62.5% >50 nmol/L	PBA
IUNA (NTFS II) 2019/20 [200]	428		50% Male	Ireland (51-55)	13-18	3.7 (3.0)			94% <10 μg	4-Day Food Diary

ELISA; enzyme-linked immunosorbent assay, LC-MS/MS; PBA; Protein Binding Assay, FFQ; Food Frequency Questionnaire, IQR; Interquartile Range, NTFS; National Teen Food Survey, NCFS, National Children Food Survey, NPSNS; National Pre-school Nutrition Survey. °N; Northern Latitude (Degrees).

1.3.3 Supplements (n=23)

Adults

Between 10-47% of Irish adults were found to be taking vitamin D supplements [78, 84, 155, 158], and received more of their intake this way than from dietary sources [68, 84]. In a recent (2019) TILDA report, just over 10% of over 7''s reported consuming a vitamin D supplement [158]. Supplement use was also a predictor of vitamin D status in older adults [46, 48, 78, 80, 158], and in most studies in adults [84, 98, 99], except one [155]. In fact, supplement use has been found to be the strongest determinant of vitamin D status in the TUDA [46] and TILDA [158] cohorts of older adults, with a mean increase of 21.4-35.4 nmol/L detected [46]. Supplementation was also found to increase with age [84, 204], with its contribution to dietary intake nearly twice as high in older adults aged 50+ (17%) versus younger adults (9%) [84]. Supplements relating to bone health (calcium with/without vitamin D) are the most consumed in older adults [67]. Irish women are more likely to take supplements than men [48, 67, 68, 78], where they contributed more to total vitamin D intake [204].

Supplement use has been reported in 25% of athletes and was a significant predictor of vitamin D status [98], with 5000 IU/day wintertime supplementation effective in preventing deficiency in early spring [99]. Vitamin D was the most consumed supplement in a cohort of adult cancer survivors (46%) [221]. Other research on the effects of vitamin D supplementation following breast cancer diagnosis has found an association with reduced mortality risk [222]. The cost/benefits modelling study of a national supplement policy for older adults (>50 years) was explored and found the greatest cost effectiveness was in those over 70 years, costing 5400 per quality-adjusted life years [223].

Pregnancy

Nearly 40% of pregnant Irish women reported taking a vitamin D supplement in a Dublin study (n=175) in 2016, though a further 57.9% unknowingly consumed a multivitamin containing vitamin D [224]. Overall, 74.3% were taking supplementary vitamin D but the study was small and confined to one area [224]. However, less supplement use in pregnancy has been associated an increased risk of low vitamin D status in Irish infants [129]. Supplementation in pregnant women in Ireland was also the strongest predictor of 25(OH)D >30 nmol/L with Caucasian females more likely to supplement than those of other ethnicities [52].

Children

The most recent national dietary survey of Irish children in 2017/2018 indicated that just 10% consume a vitamin D supplement [86]. Vitamin D supplement use was previously (2010) found to be 17% in Irish children aged 1-4 and was associated with better vitamin D status [220]. Supplement use was also reported in 23% of children in 2014 (1-17 years) and was associated with sufficient (>50 nmol/L) vitamin D status [54]. Overall, supplements are an important contributor to vitamin D status in children and adolescents in Ireland. However, use has been found to decrease with age, with 21% of 5-8, 16% of 9-12 and 15% of 13–17-year-olds consuming a vitamin D containing supplement [54, 100, 141, 220]. Since the introduction of the infant supplementation policy in Ireland, initiation of a 5 μg/day supplement from birth increased to 92%, with a third (30%) of parents fully compliant during the first year [101]. Receiving guidance from a health professional was the strongest predictor of compliance [225]. For children aged 1-5 years, 5 μg/day intake is recommended, with guidelines for older children (6-11 years) recently increased to 10 μg/day [2, 4].

1.3.4 Vitamin D Supplementation / Intervention Studies (n=14)

In pregnancy, supplementation with 5 μg/day successfully corrected poor vitamin D status (<30 nmol/L) in term infants [131]. In preterm infants with vitamin D <50 nmol/L, 10 μg/day has been shown to be effective [123]. A 20 μg/day supplement was effective in restoring sufficiency (>50 nmol/L) in mothers and cord blood [134] in a double-blind trial during pregnancy. In terms of method of delivery, oral spray has been found to be equally as effective as capsule supplementation in raising 25(OH)D [151].

In older females, a daily vitamin D (800 IU), when given alone or in conjunction with calcium, was effective in restoring vitamin D levels, with 82% achieving sufficiency (>50 nmol/L) [226]. In a similar study of men and women, daily supplementation (800 IU) increased mean 25(OH)D by 24 nmol/L, however 72% did not achieve a level above 75 nmol/L [227]. Wintertime supplementation of young adults (18-27 years) with 15 μg/day for 8 weeks was effective in raising vitamin D status but had no effect on bone turnover markers [228], similar to another study in young adults (20-40 years) and older adults (≥64 years) [229].

In an RCT, women (>65 years) given 300,000 IU intramuscular dose increased mean 25(OH)D (25.5 to 81 nmol/L), with just 11% remaining deficient post-treatment [230]. In a 10-week double blind RCT of older adults, 25(OH)D_3 supplementation was 5 times more effective in raising serum 25(OH)D compared to vitamin D_3 [231]. A 15-week double blind intervention in older adults found similar

responses to vitamin D supplementation (15 μg/day) between high and low dietary calcium groups, suggesting no interaction [232]. A 22-week RCT supplementation study of 15 μg/day found that fat mass and BMI negatively affected vitamin D status in older adults (>64 years), but not in younger adults (20-40 years) [62]. Through double blind placebo-controlled trials, it is estimated older adults (≥64 years) require between 8.6 μg/day and 24.7 μg/day to meet winter serum concentrations ≥25 nmol/L and ≥50 nmol/L respectively [37]. Similarly for adults (age 20-40) intake requirements of 8.7 μg/day for ≥25 nmol/L and 28 μg/day for ≥50 nmol/L in wintertime have been calculated [36]. While high dose (100,000 IU) intramuscular vitamin D has been found to improve markers of arterial stiffness in older adults (≥65 years) [233], supplementation up to 15 μg/day had no effect on cardiovascular markers in young adults (20-40 years) or older adults (≥64 years) [234]. The effects of 15 μg/day supplementation on metabolic parameters are mixed and vary by genetic phenotype, who found no effect on cytokine concentrations [235, 236].

1.3.5 Vitamin D Excess (n=16)

The majority of studies (n=9) investigating 25(OH)D >125 nmol/L were in adults [51, 84, 89, 119, 149, 153, 154, 156, 237], with 4 in pregnant women/babies [53, 118, 123, 133], 3 in children [89, 136, 141] and one in a MS patient [238]. The overall prevalence in population studies varied in adults (0.7-4.8%), pregnancy (0.3-9%) and children (0.4-12.1%). The recent and largest (n=100,505) cross-sectional study of adults found a prevalence of 25(OH)D >125 nmol/L of 1.9% [89]. Excess levels were lower during the COVID pandemic compared to after (1.7% vs. 2.1%, $P<0.001$), and was attributed to increased dosage of new-to-market vitamin D supplements [89]. It is estimated that up to 5% of the Irish adults in the population may be at-risk of levels >125 nmol/L, with significant increases from 0.7% to 3.8% between 1994 and 2013 [16, 149]. Most studies found a prevalence of vitamin D excess of between <1% and 3% [16, 51, 84, 119, 154, 156]. Lower levels of excess were identified in nursing homes and hospital inpatient clinics (compared to outpatients or community dwelling adults) [153] A low prevalence (0.3-0.9%) was also found in ethnic minorities, institutionalised adults, and pregnant women [51, 53, 156] who are greater risk of deficiency and possibly less likely to use supplements. Conversely, higher levels of excess were identified in Irish females (4%) and older adults (4%) [154], as found elsewhere [239, 240]. This is likely due to females being twice as likely to use supplements, especially those over 50 [67, 68]. A high prevalence of excess of 9% was identified in Irish pregnant women supplemented with up to 20 μg/day in a randomised controlled trial [118], though otherwise low levels (0.3- 0.5%) have been found in pregnancy [53, 133]. Prevalence of vitamin D excess in children was identified to be between 0.4-12.1% [89, 141], though in some studies, excess rates were low (0.4-0.6%) [136, 141] or not detected [133], but higher (4.6%) in others [89]. In babies, a prevalence of 9% was

found after 10 μg supplementation for 6 weeks [123], with none detected in another prospective study [133]. There was one report of severe hypercalcaemia (corrected calcium of 3.69 mmol/L) due to excess supplementation (10,000 IU/day for 2 years) in an MS patient who had a 25(OH)D level of 1617 nmol/L [238].

1.4 Discussion

In the first and only review of vitamin D research on the Island of Ireland, we identified 142 studies and 7 reports published between 1990 to 2022. Research in vitamin D has increased from only 3 studies in 1993-1996, 32 in 2001-2010, to 98 in the period 2011 and 2020, and a further 16 between 2021/2022. Most studies were in at-risk groups/medical conditions (n=28), dietary investigations (n=23), older adults (n=23), and with only 17 in children. The overall prevalence of deficiency (<30 nmol/L) ranged from 8% to 38% in adults [143, 148], with the highest (63-68%) teens, preterm babies, and their mothers [132, 135]. All studies found higher levels of deficiency and levels less than 50 nmol/L in winter versus summer, illustrating the seasonal variation of vitamin D synthesis. Prevalence of levels above 125 nmol/L varied from 0.3% to 9% in 16 studies that mainly include adults. The lowest intake of vitamin D was found in children (1.8 μg) and pregnant women (1.9-2.1 μg) [139, 207] with the highest in older adults (6.9 μg) (>65 years) [94].

1.4.1 Pregnancy

We found a high prevalence of deficiency (3-65%) and levels less than 50 nmol/L (7-96%) in pregnant women, with dietary intakes ranging between 2.8-10.7 μg/day. Due to increased requirements, vitamin D status deteriorates with pregnancy progression. Consequently, most babies were found to have low vitamin D at birth. Vitamin D status in pregnancy has been investigated in several other northern European countries. In Denmark, nearly one in five pregnant women had vitamin D less than 50 nmol/L [241] with approximately half in the UK [242] and Belgium [243].

A number of studies focused on maternal and foetal effects of vitamin D supplementation in pregnancy. As found in Ireland, previous systematic reviews elsewhere on vitamin D supplementation in pregnancy found a reduced risk of pre-eclampsia when combined with calcium [8]. In foetal health outcomes, previous evidence suggests reduced rates of neonatal hypocalcaemia with maternal supplementation [8], and an association with intrauterine and respiratory mortality in preterm infants [132, 244]. While vitamin D deficiency has been linked to increased fasting glucose and HOMA in Irish pregnant women, and elsewhere [245], the association with gestational diabetes

is unreliable [8]. At present, the evidence on the effects of maternal vitamin D supplementation on neonatal anthropometrics is inconsistent [8], with no correlation found with measures at birth in some [129], with some effect shown in an international review [244]. Furthermore, no conclusive evidence has been found regarding associations between maternal status and neurological and cognitive development [8, 133].

Currently there is no increased recommendation for vitamin D intake in pregnancy, with advice for those aged between 5 and 65 years to achieve 15 μg/day (diet and supplements). In Finland, the 2003 food fortification of liquid milk resulted in a significant increase in vitamin D intakes in pregnant women [246], and as such should be considered as a public health measure to improve vitamin D status in Ireland.

1.4.2 Childhood/Adolescence

Studies show vitamin D deficiency is prevalent in Irish children particularly in adolescents and during winter. Overall, approximately half of children aged 1-17 years had levels <50 nmol/L [54, 89, 108, 136, 142], similar to findings in Northern Europe at a similar latitude (47-69°N) (Table 1.9) [163, 172, 247-251]. The seasonal variation in vitamin D deficiency was evident, as has been identified in other northern locations including the UK (50°N) [90], the EU (35-60°N) [252], the Netherlands (52°N) [249] and Canada (45-70°N) [253, 254]. The UK National Diet and Nutrition Survey (NDNS) survey found 18% of children (age 1-18 years) were deficient, with more than half (53%) <50 nmol/L [163]. Adolescents (age 15-18) considered at greatest risk [163, 255], with recent report in the UK finding that 19% of 11-18-year-olds were deficient, compared to just 2% of those aged 4-10 [256]. In Sweden, vitamin D status was inversely associated with age, which was attributed to its infant supplementation policy [251]. Other suspected factors for poor status in children/adolescence is more screen time and thus sedentary behaviour, and increased obesity rates [85, 95, 257]. As adolescence represents a key period of extensive bone growth, physiological demands of vitamin D may also be higher [29, 88]. Moreover, lower rates of supplements and fortified food consumption has been found in Irish teens compared to children [100]. Due to the importance of vitamin D for bone and muscle health, maintaining adequate status is particularly important for children and adolescents. In addition, vitamin D deficiency may have an aetiopathological role in a number of extra-skeletal conditions [58, 258-264]. As such it is important that children and adolescents maintain a sufficient intake of vitamin D via dietary and supplementary sources.

Table 1.9 Vitamin D Status in Children Across Ireland and Northern Europe (>50°N)

Study	Location (°N)	N	Age range (yrs) Mean (SD)	25(OH)D Mean (SD)	%<25 (nmol/L)	%<30 (nmol/L)	%<50 (nmol/L)
KiGGS [163]	Germany (47-55)	10,015	1-17.0 9.5 (4.6)	54.0[1] (19.2)	6.0	11.9	44.5
NDNS [163]	UK (50-59)	511	1-18.0 11.6 (4.6)	48.8[1] (19.2)	12.7	18.4	53.4
Sioen 2012 [247]	Belgium (51)	357	4-11 8.1 (1.5)	47.2[5] (14.6)	5.0	n/a	58.0
Voortman 2015 [249]	Netherlands (52)	4167	6.0	64.0[2] (4-211)*	6.2	n/a	29.8
Ní Chaoimh 2018 [141]	Ireland (52)	741	1.9-2.8 2.1 (0.1)	63.4[2] (20.4)	1.6	4.6	26.7
Scully 2022 [136]	Ireland (53)	1226	1-17 15.0 (2.2)	43.8[2] (25.5)	17.0	23.0	50.6
Carroll 2014 [54]	Ireland (53)	252	1-17	51.0[2] (25.0)	n/a	21.9	54.6
McVey 2019 [139]	Ireland (53)	79	5 5.1 (0.2)	55.0[3] (29.0)**	n/a	12.7	39.2
OPUS [163]	Denmark (54-55)	779	8.4-11.6 10.0 (0.06)	56.1[1] (16.7)	2.6	6.2	36.8
Hill 2002 [137]	Northern Ireland (54-55)	1015	12, 15	64.39[4] (27.3)	3.0	n/a	36.0
Nälsén 2020 [250]	Sweden (55-69)	206	10-12 11.3 (0.5)	52.9[2] (14.3)	n/a	4.9	42.2
Andersson 2016 [251]	Sweden (55-69)	2048	1-18 8.6 (3.7)	58.4[6] (5.0-159.3)*	3.0	n/a	34.0
Holten-Andersen 2020. [265]	Norway (61)	295	0.5-18 7.8 (4.4)	70.0[3] (23.4)	1.0	n/a	22.0
Thorisdottir 2016 [266]	Iceland (63-66)	139	6.0 6.1 (0.3)	56.5[6] (17.9)	n/a	6.0	36.0
Tromsø Study [163]	Norway (69)	939	15.0-18.0 16.0 (1.0)	38.3[1] (17.7)	27.3	39.6	76.1

KIGGs, German Health Interview and Examination Survey for Children and Adolescents; Cork BASELINE Birth Cohort Study; CUH, Children's University Hospital Study; ROLO, Randomised cOntrol trial of LOw glycaemic index diet during pregnancy; NDNS, National Diet and Nutrition Survey (NDNS): Years 1-4 (combined) of the Rolling Programme (2008/2009-2011-2012); OPUS, Optimal well-being, development and health for Danish Children though a healthy New Nordic Diet School Meal Study; Tromsø Study, Fit Futures. 25-hydroxy-vitamin D (25(OH)D) Quantified by; (1) VDSP-LC/MS Vitamin D Standardisation Programme, (2) Liquid Chromatography Mass Spectrometry, (3) Protein Binding Assay, (4) Enzyme-Linked Immunosorbent Assay. (5) Radioimmunoassay (6) Chemiluminescence immunoassay. Reported as *Median (Range) or **Median (IQR)

1.4.3 Adults (<50 years)

Vitamin D deficiency was prevalent in Irish adults, particularly in younger adults and in winter. Several meta-analyses have investigated vitamin D status in Europe [50, 163, 172] with deficiency ranging between 5-35% and levels less than 50 nmol/L ranging between 34-64% with highest prevalence in Scotland [56, 163, 267, 268]. Despite not generally being considered an 'at-risk' population, several studies in Ireland indicate that vitamin D deficiency is prevalent in younger adults more so than older adults [25, 148, 149, 154-156]. This nadir has been reported in Romania [269], Canada [270], the US [271], and Brazil [272]. Lack of sunshine exposure due to time spent indoors in a working environment and reduced dietary and supplementary intakes of vitamin D may be factors [84, 94, 273].

Low vitamin D status was more prevalent in the winter, with up to 58% of the Irish population <50 nmol/L [25, 143, 154, 155]. Previously, a 25 nmol/L difference in 25(OH) serum concentrations between the late winter nadir and summer peak has been identified, coinciding with UVB availability [274]. As vitamin D production is limited above 40°N between October and March, many European populations are at-risk of low status in the winter [172]. As a result, there exists a North-South gradient of vitamin D production, except for some Nordic countries, where oily fish consumption and supplementation is common [63]. Similarly in a global study, no overall effect of latitude was found with variations in vitamin D status explained by intake, cultural, genetic, and methodological factors [275].

In general, Irish studies have found that women had higher serum 25(OH)D than men. While this finding contrasts a Southern European study, it is in keeping with a large global meta-analysis which found that females had a borderline significantly increased vitamin D status compared to males [275, 276]. This finding may be explained as Irish women are twice as likely to consume a supplement and are more likely to be taking vitamin D orally than men [67, 68, 84].

1.4.4 Older Adults

Several studies found that vitamin D deficiency is prevalent in older Irish adults, with most large studies ranging between 8-32%. Deficiency levels detected as part of the TILDA and TUDA studies are in keeping with an EU meta-analysis which found 13% of adults had 25(OH)D <30 nmol/L [163]. In the UK ELSA study, higher levels of inadequacy were found with 26% of older adults (>50 years) deficient, and 59% <50 nmol/L [57]. Lower levels have been detected in older adults in the Netherlands, Iceland, and in Sweden [163, 277, 278], potentially due to cultural differences in diet and supplemental intakes and genetic adaptations to limited UV availability [50, 277]. Women were more

likely to be deficient in Germany [279], the UK [57] and the Netherlands [280]. This contrasts with studies in Ireland, which found greater sufficiency in older females [48, 78], which may be due to increased supplementation and fortified food intake [78, 84]. Vitamin D deficiency is more prevalent during winter in Ireland [48, 140, 143, 160]. Despite a reduced capacity for dermal synthesis, UVB light and sun enjoyment are important determinants of vitamin D status in older Irish adults [78]. Low vitamin D status has been detected in other European countries of similar latitudes [57, 80, 163, 267], with more than 50% having levels <50 nmol/L [50].

Up to 75% of Irish adults were found to have levels less than 50 nmol/L [165], with rates varying by season and location. Similar findings were reported in the UK English Longitudinal Study of Ageing (ELSA) where 59% had levels <50 nmol/L [57]. In other European countries of similar latitudes, up to 50% of older adults (>50 years) also had levels <50 nmol/L, with a higher prevalence in those who were institutionalised [50, 80, 163].

Predictors of low vitamin D in Ireland included smokers, physically inactive individuals, obese, non-supplement users, males, and those over 80 [48, 57]. Positive determinants included sun holiday travel, summer season, UVB exposure, sun enjoyment, and fortified milk consumption [46, 48, 57], with supplement use considered the strongest predictor, particularity in the oldest old [46, 281]. Daily yoghurt intake, but not milk or cheese was a positive predictor of vitamin D status [282]. Engaging in physical activity, a potential proxy measure of outdoor sun exposure, has also been found to be a determinant of vitamin D status in older populations in Ireland [48], the UK [57], Denmark [283] and the Netherlands [284].

Older adults occupying northern locations presenting with higher rates of inadequacy [48], with similar evidence has been found in the UK [57] and Germany [279]. As found in the UK [57], older adults in urban locations had increased rates of deficiency and levels <50 nmol/L [156]. Non-community dwelling individuals were at increased risk of low vitamin D in Ireland [156], in the UK [285], in Austria [286], in Sweden [287] and across Europe [288]. This is likely due to reduced physical activity, lack of sun exposure and poor adherence to supplementation recommendations [288, 289].

1.4.5 At-Risk Populations

We found the highest prevalence of deficiency (67%) and levels less than 50 nmol/L (93%) in Southeast Asians [51]. Ethnic minorities living in northern locations are at increased risk of low vitamin D status due to reduced efficiency of cutaneous synthesis [50, 172]. This is in keeping with the

UK where 96% of Southeast Asian women had levels <50 nmol/L in winter and had lower serum 25(OH)D compared to Caucasian women [290]. Similarly non-European populations living in Europe were at greater risk compared to their indigenous counterparts [291]. As found in Ireland [52, 53], pregnant women of non-European descent are at substantially increased risk of low vitamin D status as in the UK [292], the Netherlands [293] and Norway [294]. Irish children of African ethnicity also had significantly lower vitamin D status than other ethnicities, as found in the UK [295]. In a modelling study it has been estimated a daily intake of 27.3 μg (1092 IU) and 33.2 μg (1328 IU) is required to preventing winter deficiency in 97.5% of individuals of South Asian and Black ethnicity at Irelands latitude [296]. However, this may be difficult to achieve without supplementation, with lower rates of supplementation found in Ireland, as found elsewhere [297].

Others at-risk of low vitamin D include those with Crohns Disease where prevalence was 18-64%, particularly in winter months [173] and with 90% <80 nmol/L [71]. Comparatively in the UK, 66% had had serum concentrations <50 nmol/L, with significantly lower status in the winter [178]. Crohn's patients who had IBD related surgery were three times more likely to have vitamin D <50 nmol/L, with non-Caucasians also at increased risk [178]. Similar results were found in the Netherlands, where 81% had serum 25(OH)D <75 nmol/L [298], predicted by no sunny/active holiday, high sun protection behaviours, non-Caucasian ethnicity [298]. In addition, a meta-analysis revealed that Crohn's patients had lower vitamin D status than healthy controls, with more than half less than 50 nmol/L, and was significantly correlated with latitude [177].

Up to 40% of children with autism had levels <50 nmol/L and 75% <75 nmol/L [193, 196], consistent with a meta-analysis in 2016 that attributed lower status to factors such as increased dietary restriction and lack of time outdoors [299]. In Irish patients with MS, a latitudinal variation in prevalence was found, with higher levels in the Northeast compared to the Southwest [180]. MS occurrence has previously found to increase with latitude and is associated with reduced UVB exposure and serum vitamin D [300]. Maintaining serum >100 nmol/L might reduce MS prevalence [301], however, in patients with Clinically Isolated Syndrome (CIS), a precursor of MS, no correlation was found [181].

Due to its role in immune function and lung development, vitamin D in asthma and COPD was explored [302]. In Ireland, half of asthmatic children had vitamin D levels <50 nmol/L [194]. This is in keeping with a global meta-analysis which found lower status in children with asthma compared to healthy children [195]. Poor vitamin D status in asthma has been linked to decreased quality of life

[302], with supplementation linked to reduced risk of asthma attacks [195, 303]. In Belfast, vitamin D status was low in COPD patients, particularly in winter and in house-bound patients and having a significant effect on muscle strength and quality of life [188]. Higher vitamin D levels correlated with improved lung function and quality of life [304], with lower concentrations associated with disease severity and future risk of exacerbation [302]. Poor vitamin D status and sleep apnea have several correlated risk factors such as obesity, winter season and ethnicity, and are thought to be interlinked due to vitamin D's role in inflammation and immunity modulation [189, 305]. The finding in Ireland that sleep apnea patients have high rates of levels below 50 nmol/L has been confirmed in a global meta-analysis, which found disease severity was exacerbated with decreasing vitamin D status [306].

1.4.6 Dietary

The first dietary survey in Irish children aged 12-59 months found 70-84% had intakes less than 5 μg/day [94]. In 1 year olds, milk/formula contributing 29% of total intakes [96], with identical levels found in UK children aged 12-18 months [307]. Similar to Ireland, milk/products were the greatest source followed by meat and its products in UK children under 4 [96, 307]. A recent nationally representative survey of children (5-12 years) and teens (13-18 years) found the majority (94%) had intakes less than 10 μg/day, with little improvement compared to previous reports [85, 86]. This is similar to findings in the UK which found mean intakes in children was a fifth of the recommendation (10 μg/day) [308].

The first National Adult Nutrition Survey (NANS) in 1999 indicated the Irish population had inadequate mean intakes of vitamin D, with little improvement in its follow up, with 90% of adults not meeting recommended intake of 10 μg/day [94, 202]. Pregnant women also had inadequate intakes, with 80-99% not meeting this level [207-209, 219]. In the UK, comparatively high levels of inadequate intakes were found, with between 98-100% not meeting the recommended level of 10 μg/day [309]. Despite its relatively low content, meat, and its products accounts for the primary source of vitamin D for the population over 13 years. This is reflected in the UK, where it contributes 35% of dietary intake, with milk/products also playing an important role [8]. Fortified cereal/products contribute between 13-20% of the UK populations dietary intake [8], and 10% in the Irish diet [310]. The main contributor of dietary vitamin D to the adult population varies across Europe, with fats and meat/products being the main sources in the Netherlands, with fish and eggs the primary and secondary sources in France and Spain [172, 311, 312].

Overall, vitamin D intake in Ireland ranged from 2.3 μg/day in children to 6.9 μg/day in older adults (>65 years), with adults (18-64 years) having intakes of 4.3 μg/day [94, 198]. Dietary intakes in pregnant women ranged between 2.8-10.7 μg/day [125, 209]. These intakes are similar to those reported in the UK, Germany, Denmark, and the Netherlands, though higher than in Portugal, Spain, and Italy [50]. By comparison, dietary intakes have been found to be higher in Northern European countries such as Iceland, Norway, Sweden, and Finland [50, 313]. In Ireland the RDA in pregnancy is no different than the general adult population at 10 μg/day [314]. However, evidence suggests that pregnant women require 20 μg/day to meet sufficiency (>50 nmol/L) [134] with 10-15 μg/day advised by a European consortium [50]. In Finland, the 2003 food fortification of liquid milk resulted in a significant increase in vitamin D intakes in pregnant women [246], and as such should be considered as a public health measure to improve vitamin D status in Ireland.

1.4.7 Supplements

Between 10 and 47% of Irish adults and older adults were found to be taking vitamin D supplements [78, 84, 155, 158]. From national dietary data, the contribution of supplements to dietary intake is nearly twice as high in older adults (17%) than adults (9%) [84]. Higher levels of supplement use were shown with increasing age [84, 204], as shown elsewhere [315], with similar levels in UK adults (14-19%) and older adults (24-32%) [309]. Supplement use was a predictor of vitamin D status in older adults [46, 48, 78, 80, 158], and most studies in adults [84, 98, 99], apart from one [155]. Supplementation has been found to improve vitamin D status independent of age, sex, or ethnicity [50]. Women are more likely to take supplements than men [48, 67, 68, 78]. Supplements contributed more to total vitamin D intake compared to men [204], particularly in older females [158], as reflected in research from the UK [316]. Irish adults with the highest vitamin D intake were found to have increased risk of oesophageal adenocarcinoma in one case-control study [317].

Despite the WHO advising against routine pregnancy supplementation, 10-15 μg/day has been advised by a European consortium [50]. In Ireland the level of supplementation recommended in pregnancy is no different than the general adult population at 15 μg/day [4]. However, evidence suggests that 20 μg/day is required for maternal and infant levels to meet sufficiency (>50 nmol/L) [134]. In the UK, while 20 μg/day supplementation significantly improved vitamin D status, just 30% of women achieved sufficiency (>50 nmol/L) [318]. Evidence indicates that three quarters of Irish pregnant women are knowingly and unknowingly supplementing with vitamin D, with 28% unaware of the recommendations [224]. Supplementation in pregnancy was the strongest predictor of 25(OH)D >30 nmol/L, with Caucasian women more likely to supplement than women of other

ethnicities [52]. While just 28% of a pregnant population was found to be supplementing with vitamin D in the UK, no difference was found by ethnicity [319].

Children aged 1-5 are recommended to receive 5 μg/day, supplementing if necessary, with older children (age 6-11 years) to get 10 μg/day and adolescents (>12 years) advised to get 15 μg/day [2, 4]. Across Europe, there are varying recommendations for children aged 4-10 and 11-18, ranging between 5 and 25 μg/day [50], with another report indicating 15 μg/day for children/adolescents without risk factors [39]. Several reports in Ireland found approximately 10-20% of children are supplemented, with a decreasing rate of use with age [54, 100, 141, 220]. Similar findings have been reported in the UK, with higher supplementation rates in children (14-16%) compared to teens (5-6%) [309]. Supplements are an important contributor to vitamin D status in children and adolescents [54, 220], as found elsewhere in Europe [252, 320, 321].

1.4.8 Intervention / Supplementation

Intervention / supplementation studies have explored factors including dose, method, vitamin D type, and the combination with calcium. Supplementing with 800 IU/day (15 μg/day) significantly increased serum 25(OH)D in older Irish adults [227], as confirmed elsewhere [322]. An 8.6-8.7 μg/day dose was estimated to avoid wintertime deficiency (<25 nmol/L) in adults and older adults [36, 37]. However, body composition may role in supplementation efficacy in older adults, as fat mass and BMI negatively influenced status, but not in younger adult [62]. Previously it has been found that vitamin D is sequestered in adipose tissue [29], and so increased body fat with age may hinder bioavailability [323].

Supplementing by an oral spray was equally effective as capsule supplementation [151] as confirmed by a recent systematic review [324]. A 300,000 IU intramuscular dose was successful in restoring sufficiency in older Irish adults [230], and is beneficial in acute care and non-compliance with oral medication [325]. Vitamin D type should also be considered, as 25(OH)D_3 was more effective in raising serum 25(OH)D compared to vitamin D_3 [231]. Vitamin D supplementation does not appear to interact with calcium as status was restored when 800 IU was given with or without with calcium, and in high and low dietary calcium consumers [226, 232].

The effect of vitamin D supplementation on bone, muscle and cardiovascular health in Irish adults has been explored with mixed results. Supplementing with 15 μg/day improved markers of arterial stiffness but had no effect on cardiovascular health [233, 234]. Evidence for supplementation and

cardiovascular health was determined to be inconsistent in a systematic review and a SCAN report [8, 326]. Similarly for metabolic health, while certain phenotypes may be responsive, cytokine concentrations were unaffected [235, 236]. The benefits of adequate vitamin D status on bone health are well established [8], however there was no change in bone markers in young and older adults given 15 μg/day [228, 229]. In one study, the short supplementation (8 weeks) may explain the lack of effect as 3 months minimum is required for the therapeutic action of vitamin D [228, 327]. In addition, the level of supplementation may be inadequate as up to 28 μg/day may be needed to achieve sufficient serum concentration (50 nmol/L) [36].

1.4.9 Excess

Up to 5% of the Irish adult population may be at-risk of excess levels (>125 nmol/L) of 25(OH)D, with significant increases between 1994 and 2013 [16, 149]. The range was 0.3% and 12.1% and was greatest in infants and those taking supplements, with one case reported of hypercalcemia (25(OH)D 1617 nmol/L, Corrected Ca 3.69 mmol/L). The prevalence of levels >125 nmol/L increased between the year before the COVID pandemic to during, and was attributed to increased dosage of new-to-market vitamin D supplements [89]. Higher levels of excess vitamin D were identified in Irish females (4%) and older adults (4%) [154], as found elsewhere [239, 240]. This is likely due to females being twice as likely to use supplements, especially those over 50 [67, 68]. This was found in the US, where 8.4% had levels in excess of 125 nmol/L, a significant increase between 2002 and 2011 [239]. This was attributed to increased dietary vitamin D intake, from fortified food and greater supplement use/dosage [16, 239]. On the other hand, prevalence of excess 25(OH)D (0.3-0.9%) was lower in ethnic minorities, institutionalised adults, and pregnant women [51, 53, 156] who are greater risk of deficiency and possibly less likely to use supplements. While most studies report low vitamin D status, fewer reported levels above 125 nmol/L.

1.4.10 Implications for Public Health

Evidence from Ireland indicates that low vitamin D status is prevalent, affecting up to 67% Southeast Asians, 65% pregnant women and 23% of children, particularly adolescents. Just one study focussed specifically on an ethnic population [51], with research lacking in non-Europeans and minority groups such as Irish Travellers and institutionalised adults including prisoners [114]. In light of low vitamin D intakes in the homeless population and with nearly 9,000 people in emergency accommodation in Ireland, consideration should also be given to this group [328, 329]. The effects of changing dietary patterns on vitamin D status should also be investigated as nearly 1 in 5 Irish adults are vegetarian or vegan [330]. As meat is the primary dietary source of vitamin D,

vegans, and those with restricted diets with limited sources of vitamin D may be at-risk of deficiency [94]. Thus, research in this population group would be useful. In addition, more robust evidence, such as double blind RCTs, are required before the link between vitamin D and extra-skeletal health can be confirmed. However, with confirmed benefits for bone health and plausible benefits for immune function, optimising vitamin D intake to recommended guidelines is advisable [43],

Previous gaps in guidelines for at-risk groups including pregnant women, adolescents, and dark-skinned ethnicities were recently addressed by the FSAI, recommending a vitamin D intake of 15 μg/day [4]. To avoid deficiency in most of the population an intake of 12 μg/day has been calculated [201]. However, preventing winter deficiency in 97.5% of individuals of South Asian and Black ethnicity at Irelands latitude may require an even higher respective daily intake of 27.3 μg (1092 IU) and 33.2 μg (1328 IU). An intake of 25-28 μg/day may also be needed to maintain wintertime sufficiency in the Irish population (>50 nmol/L) [36, 37]. Though achieving this via diet alone is not possible and adherence supplements poor, thus vitamin D fortification of staple foods should be considered. Indeed, diet modelling studies in older adults have indicated that fortification of bread and milk would allow 70% to meet the RDA [216]. In pre-school children, it has been found that both fortification of cow's milk and a low dose supplement would be required to reduce inadequate intakes for the majority [211]. Another study found just one scenario (Follow-up Formula + Fortified drink + supplements) where children could meet the EFSA RDA of 15 μg/day [212]. In 2003, mandatory fortification of butter/spreads and milk products in Finland enabled 91% of the population to reach sufficiency by 2011 [218]. However, some groups of the population consume less fortified foods and are less likely to benefit [331]. Exploring a multi-food system approach that includes fortifying bread in addition to dairy products could be considered to target a wider population [172].

1.4.11 Strengths & Limitations

This is the first comprehensive and scoping review of all studies on of vitamin D status, intake, and supplementation on the island of Ireland. We included a wide variety of studies and reports, that encompassed all research published between 1990-2022 across numerous study types, populations, and diseases. We also included nationally representative reports. However, it is not a systematic review and we excluded published abstracts, non-peer reviewed articles and studies published prior to 1990.

1.5 Conclusion

This review indicates that low vitamin D status is not confined to one demographic and is widespread throughout the population. The overall prevalence of deficiency (<30 nmol/L) ranged from 8% to 38% in adults [148, 154], with the highest (63-86%) in older adults, teens, preterm babies, and their mothers [132, 135]. The seasonal variation of vitamin D production was evident with higher levels of deficiency and prevalence of levels <50 nmol/L in winter versus summer. The lowest intake of vitamin D was found in children (2.2 μg/day) [220] and pregnant women (1.9 μg/day) [207] with the highest (6.9 μg/day) in older adults [94]. In particular, children, adolescents, younger adults, pregnant women, and ethnic minorities are at-increased risk of low vitamin D, notwithstanding other vulnerable populations, such as institutionalised adults for which further research is needed. Given the prevalence of widespread deficiency, an updated public health policy to increase vitamin D intake, including a vitamin D awareness campaign and fortification of key food groups frequently consumed by the population may be required.

Chapter 2: Methods

This chapter provides information on the methods used for the two studies which form the basis of this thesis. This includes a retrospective cross-sectional analysis of 25(OH)D biochemical data (Lab Analysis of Vitamin D (LAVID) Study) (Chapters 3-5), and a stratified sample questionnaire study (Evaluation of Vitamin D (EVID) Study (Chapter 6).

2.1 Ethical Approval

Study 1 (Chapters 3-5)

The joint research ethics committee at St James's Hospital/Tallaght University Hospital (SJH/TUH) granted ethical approval for this study (Ref: 5475) which was conducted according to the guidelines laid down in the Declaration of Helsinki 1964. A copy of the ethical approval letter and amendments are provided in Appendix Section A (i).

Study 2 (Chapter 6)

Ethical approval for this study was granted by the St James's Hospital/Tallaght University Hospital (SJH/TUH) joint ethics committee (Ref: 5658). This study was conducted according to the Declaration of Helsinki. Copies of the ethical approval letter, amendments and participant documents are provided in the appendix Section A (ii) and Section B (i-iii), respectively.

2.2 Serum 25(OH)D and Biochemical Markers

Vitamin D (total 25(OH)D2 and 25(OH)D3) was measured using liquid chromatography tandem mass spectrometry (LC-MS/MS) (API 400; AB SCIEX) at the Biochemistry Department of SJH. A validated method (Chromsystems Instruments and Chemicals GmbH; MassChrom 25-OH-Vitamin D3/D2) accredited to ISO 15189:2012 standards was employed for analysis. Assay quality was ensured by participation in the vitamin D External Quality Assessment Scheme (DEQAS) and assay of internal and third-party quality controls and has been accredited by the Irish National Accreditation Board (INAB). The vitamin D results fell within 3.5% of the target control value, and this was similar for all years during the study. Accuracy was determined using National Institute of Standards and Technology (NIST) 972 25(OH)D standard reference material (SRM 972). The limit of quantification was 9 nmol/L, with values below this assigned as 9 nmol/L. The respective inter- and intra-assay coefficients of variation are 5.7% and 4.5%. Vitamin D cut offs were defined according to the NAM as deficiency; <30 nmol/L, insufficiency; 30.0-49.9 nmol/L and sufficiency;

≥50 nmol/L [29, 154]. Serum 25(OH)D ≥125 nmol/L were also identified as this level may constitute vitamin D excess and has been associated with some adverse health outcomes [29, 31].

2.3 Data Collection

St James's hospital (SJH) is the largest academic teaching hospital in the Republic of Ireland serving a population of approximately 350,000 people. It is located in Dublin city, on the east coast of Ireland (53.35° North latitude) and receives the majority of referrals from Dublin city and the greater Dublin area. A search was completed for vitamin D requests from Primary Care GPs at the SJH Biochemistry Department via its information system (iSOFT Telepath®). Samples requested between 2014-2018 (inclusively) were selected for a retrospective cross-sectional analysis. The exclusion criteria were; aged <18 years, missing or incomplete demographic data, non-community dwelling address (e.g., nursing home or hospital) or address outside of the Republic of Ireland.

2.4 Statistics

Statistical analysis was carried out using SPSS (Version 24, IBM Corp., Armonk, NY, USA.) Data were checked for normality by the Kilmogorov-Smirnov test and Q-Q plot and transformed where necessary. Data reported in tables and maps are expressed as geometric mean with standard deviation (SD). Categorical variables were tested using Chi-squared, with independent sample t-tests, ANOVA and Kruskal-Wallis test for continuous variables as appropriate. Statistical significance was accepted when $P < 0.05$.

Chapter 3: Geomapping Vitamin D Status in a Large City and Surrounding Population - Exploring the Impact of Location and Demographics

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The PDF of this manuscript can be found in Appendix C (ii): Thesis-related Publications

3.1 Introduction

Vitamin D has become the focus of increased interest globally, with the number of web searches rising year on year, peaking in the winter, and now eclipsing that of vitamin C [332]. Vitamin D has an established role in maintaining normal bone health, and more recently, research has demonstrated associations with chronic conditions such as diabetes [333], inflammation [40], cardiovascular disease [334], depression [169] and cancer [335].

Vitamin D is the only vitamin that can be synthesised endogenously via the action of ultraviolet-B (UVB) light on the skin. Geographical latitude, time of year, cloud cover, sunscreen use, skin pigment, obesity, religious dress, and age can all affect UVB vitamin D synthesis, making it a highly variable source [8, 10]. In locations greater than 30° North or South latitude, a 'vitamin D winter' exists between October and March when little or no vitamin D can be produced due to limited UVB penetration [336]. During this period, we rely on vitamin D through diet alone though in countries such as Ireland, where there is no mandatory vitamin D fortification of foods, it is difficult to reach the recommended daily intake (10 μg/day) as sources in the diet (such as oily fish) are limited or are often not consumed [84]. As a result, a significant proportion of the population are at risk of deficiency (25-hydroxyvitamin D {25(OH)D <30 nmol/L}) [29]. In particular, those most at risk include indoor or night shift workers [273], housebound or non-community dwellers [153], or the elderly with reduced capacity for cutaneous synthesis [48].

It is difficult to compare studies of vitamin D status as they involve different populations and thresholds for defining deficiency. In Ireland, the National Adult Nutrition Survey (n = 1,132) found that 21% of 18-84-year olds were deficient (<30 nmol/L), although this included a small number of older adults [84]. The only other nationally representative Irish study was The Irish Longitudinal Study on Ageing (TILDA) (n = 5,356), which found that 13.1% were deficient (<30 nmol/L), rising to 23% in the winter [48]. One study of Irish rural and urban dwellers (n = 17,590) identified that 15.9% of adults were deficient (<25 nmol/L) but included only those in the West of the country [156]. The Trinity Ulster Department of Agriculture (TUDA) Study of older Irish adults (>60 years, n = 4,444) reported that between 13.8 to 43.6% were deficient (<30 nmol/L), though had participants from disease defined cohorts [46]. However, it is not only older adults who are at risk. For example, in a study of adolescents across 9 EU countries 15% were deficient (<27.5 nmol/L) and 27% insufficient (27.5–49.9 nmol/L) [337].

Environment is an important determinant of health and when combined with other data can be used to create geomaps. To date, few studies have applied this technique when exploring vitamin D status. Of note, geo-mapping of a large urban area in Calgary, Canada identified population clusters where education and immigration status were the strongest predictors of 25(OH)D [270]. Moreover, vitamin D status has also been geomapped in a population of free-living adults in Dublin, Ireland (53 °N). That study found that 15.2% were deficient (<30 nmol/L) in winter, improving to 10.8% in the summer, but with significant variation by postal code area [25]. However, vitamin D measurement was limited to a one-year period.

The current study aims to investigate the vitamin D status of community dwelling Irish adults over a 5-year time period (across a broad age range) living in Dublin and surrounding areas who had their vitamin D tested in Primary Care by request of their General Practitioner (GP). A key objective is to explore the effects of sex, age, season, and geographical area on vitamin D status. Finally, in what is the largest study of its type in Europe, we aim to create a geomap that visually depicts the prevalence of vitamin D deficiency by location.

3.2 Methods Particular to this Chapter

Detailed methods regarding Ethical Approval Serum 25(OH)D Measurement and Statistical Analysis are outlined in Chapter 2, Sections 2.1, 2.2 and 2.4, respectively. Methods specific to this chapter are presented below.

3.2.1 Data Collection

Methods for the collection of data is outlined fully in Section 2.3. In this chapter, repeat vitamin D results were excluded to avoid pseudo-replication, to limit potential interference from treatment for vitamin D deficiency between samplings.

3.2.2 Statistical Analysis

Postal districts with smaller populations (n<100) but adjacent to each other and with similar demographics were combined for the analysis (D6/D6W, D13/17 and D14/16). Multinomial regression was used to explore the determinants of 25(OH)D status including age, sex, season of sampling and geographical area. The areas of 'rest of Leinster' and 'rest of Ireland' were combined to form 'outside Dublin' as the reference area. An ANOVA analysis was used to identify mean differences in 25(OH)D between areas in the winter and summer, and cluster maps were created. These depict differences between 25(OH)D across several areas, categorised with equal distribution based on median values for Winter (<10 nmol/L, 10-20 nmol/L, >20 nmol/L) and Summer (<10 nmol/L, >10 nmol/L). Seasons were defined as winter: (December, January, February); Spring: (March, April, May); Summer: (June, July, August); Autumn: (September, October, November).

3.2.3 Geomapping of Participants

Dublin area postal codes were used to record participants residence. Dublin areas are represented by postal codes (D1 to D24) with odd numbers for locations in North Dublin and even numbers in South Dublin. Some locations have no postal code but a specific name or are known only as being in north or South. County Dublin was also categorised into three main areas: North Dublin (D1, D3, D5, D7, D9, D11, D13/17, North County Dublin); South Dublin (D2, D4, D6/6W, D8, D10, D12, D14/16, D18, South County Dublin); West Dublin (D15, D20, D22, D24, Lucan). County Kildare was split into north (including the towns of Leixlip, Maynooth, Celbridge, Kilcock) and rest of Kildare. Residents in Counties Meath and Wicklow were also designated separately. Participants living in the province of Leinster (but not in Dublin or adjacent counties of Meath, Kildare, and Wicklow)

were classified as 'rest of Leinster'. Those residing outside of the above locations were categorised as 'rest of Ireland'.

A colour-coded map was created depicting the prevalence of deficiency for the areas sampled in the seasons of summer and winter, with categorisation based on the prevalence rates of 25(OH)D <30 nmol/L as follows; <10%, 11-20%, 21-29% and >30%. Areas with smaller numbers (n<120) that were likely to be non-representative were excluded from our map.

3.3 Results

3.3.1 Demographics

There were 51,651 serum 25(OH)D results reported to primary care GPs between 2014-2018, of which 36,466 (70.6%) met the inclusion criteria. (Figure 3.1). The population and area demographics are shown in the respective Tables 3.1A & 3.1B. There was a relatively even distribution of samples across all seasons. The median age was 50.7 years, ranging from 18 to 109 years. We sampled 28 areas, with requests from County Dublin and Kildare comprising the majority (97%). Approximately 15 areas had 25(OH)D results for at least 500 people, Dublin 13/17 being the smallest (n=107) and north Kildare the largest (n=5,734). Those in Dublin 1 were the youngest (35.9 ± 11.6 years) with 88% aged under 50 years, while those in Dublin 20 were the oldest (57.8 ± 17.5 years). The majority of requests (72%) were for females. This varied by location, ranging from 64% in Dublin 20 to 80% in Dublin 3.

The 25(OH)D geometric mean was lowest in winter (46.8 ± 30.3 nmol/) and highest in autumn (63.0, ± 29.4 nmol/L) versus spring (48.9 ± 30.4 nmol/L) or summer (58.6 ± 30.5 nmol/L). Females had higher 25(OH)D versus males (55.1 ± 31.3 nmol/L vs. 49.7 ± 29.0 nmol/L, P<0.001)

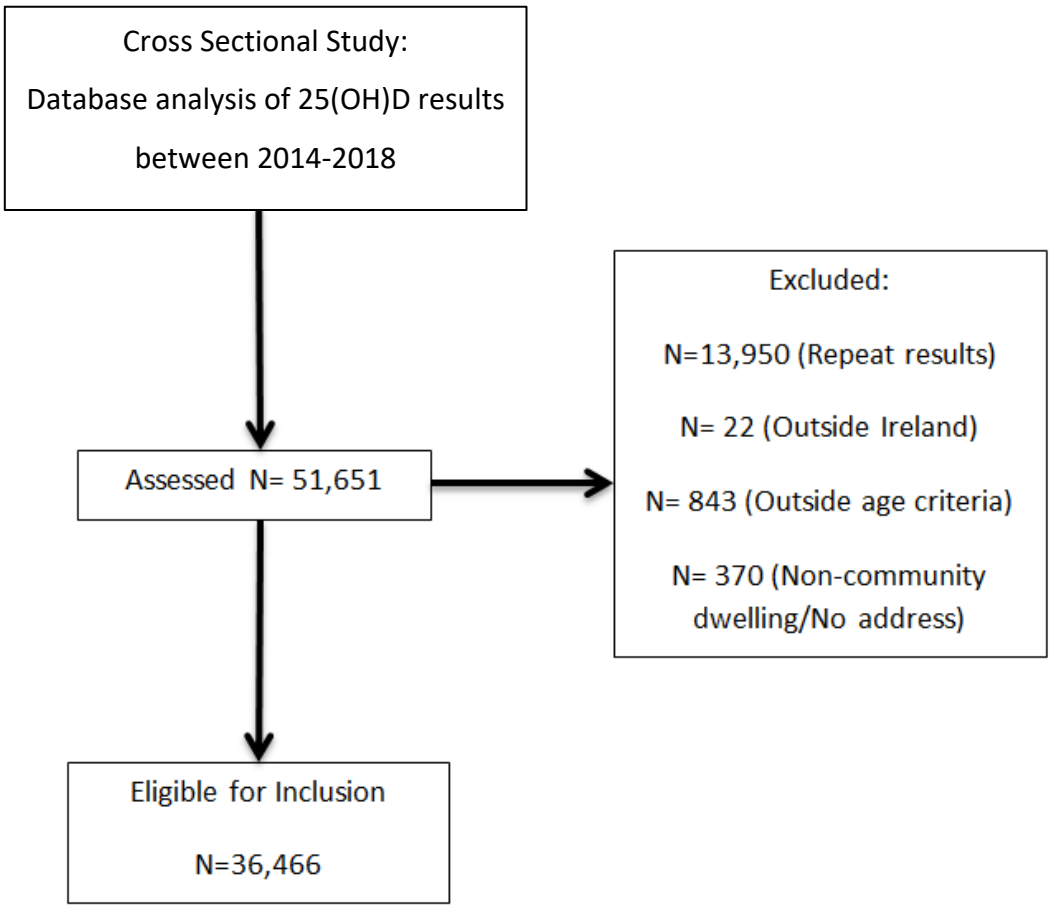


Figure 3.1 Recruitment Flow Diagram

Table 3.1A Demographics

Demographics		N	%	GM Mean (SD)
Age Category (years)	18-39	11319	31	47.8 (30.8)
	40-49	6977	19	50.3 (28.5)
	50-59	6328	17	56.5 (29.9)
	60-69	5753	16	62.1 (30.0)
	70-79	3865	11	61.7 (31.8)
	80-89	2003	5	58.1 (33.0)
	>90	221	1	54.1 (33.7)
Age groups (years)	<50	18941	52	48.8 (29.8)
	>50	17525	48	59.7 (30.8)
Area	North Dublin	1758	5	50.8 (30.9)
	South Dublin	18827	52	54.5 (31.7)
	West Dublin	8310	23	50.6 (30.3)
	Outside Dublin	7571	21	55.8 (29.5)
Season	Winter	8101	22	46.8 (30.3)
	Spring	10321	28	48.9 (30.4)
	Summer	9353	26	58.6 (30.5)
	Autumn	8691	24	63.0 (29.4)
Sex	Male	10335	28	49.7 (29.0)
	Female	26131	72	55.1 (31.3)
Total		36466		53.8 (30.78)

GM Mean (SD); Geometric Mean (Standard Deviation)

Table 3.1B Area Demographics

Area	N	GM Mean (SD)	<50yrs (%)	Female (%)
Dublin 1	290	45.5 (31.4)	88	73
Dublin 2	639	49.5 (29.6)	74	72
Dublin 3	219	54.9 (33.5)	78	80
Dublin 4	662	58.8 (33.0)	57	74
Dublin 5	111	54.6 (30.7)	75	77
Dublin 6/6W	5273	58.6 (31.1)	44	76
Dublin 7	496	51.4 (31.5)	80	74
Dublin 8	2915	49.1 (31.9)	61	74
Dublin 9	173	51.0 (29.5)	77	79
Dublin 10	846	50.8 (30.5)	42	72
Dublin 11	142	46.2 (27.3)	86	75
Dublin 12	3375	54.1 (31.8)	36	76
Dublin 13/17	107	52.0 (35.9)	82	78
Dublin 14/16	4129	59.9 (30.8)	36	70
Dublin 15	480	50.3 (31.5)	75	70
Dublin 18	372	54.0 (36.9)	72	66
Dublin 20	1353	54.3 (29.8)	34	64
Dublin 22	719	49.8 (29.5)	61	68
Dublin 24	750	52.3 (30.1)	58	73
North Co. Dublin	220	50.7 (27.7)	77	79
South Co. Dublin	616	55.9 (29.7)	58	72
Lucan, Co. Dublin	5008	46.5 (30.8)	64	69
North Co. Kildare	5734	56.1 (27.5)	49	68
Rest of Kildare	757	56.5 (29.0)	52	69
Co. Meath	502	56.2 (31.3)	66	75
Co. Wicklow	164	58.2 (28.8)	58	71
Rest of Leinster	209	54.1 (29.9)	67	72
Rest of Ireland	205	53.8 (30.5)	78	70
Total	36466	53.8 (30.8)	52	72

GM Mean (SD); Geometric Mean (Standard Deviation)

3.3.2 25(OH)D Status by Year, Age and Sex.

The 25(OH)D status over the five-year period is shown in Table 3.2, with the proportion in each category (deficient, insufficient and >125 nmol/L) split by age and sex. Overall, there was a 38% increase in vitamin D testing from 2014 to 2018. The proportion who were deficient, insufficient and who had 25(OH)D >125 nmol/L was relatively stable over time at 15%, 23% and 3% respectively. When dichotomised by age, we found that those <50 years had a higher level of deficiency versus those ≥50 years (18% vs. 11%, $P<0.001$).

Those aged ≥50 years were more likely to have a 25(OH)D >125 nmol/L (4% vs. 2%, *P*<0.001) as were females (3% vs. 2%, *P*<0.001) and those sampled in the summer (*P*<0.001). Overall, the prevalence of deficiency was greater in males versus females (17% vs 14%, *P*<0.001) as was insufficiency (27% vs. 22%, *P*<0.001).

Figure 3.2 illustrates 25(OH)D status in various age categories. Those who were youngest (18-39 years) had the highest prevalence of deficiency (21%) and insufficiency (26%). This prevalence was only matched by those in the very oldest age group (>90+ years). In fact, there was a 'U' shaped relationship, with the best vitamin D status in those aged 60-69, and then progressively declining when moving towards both the younger and older ends of the age spectrum.

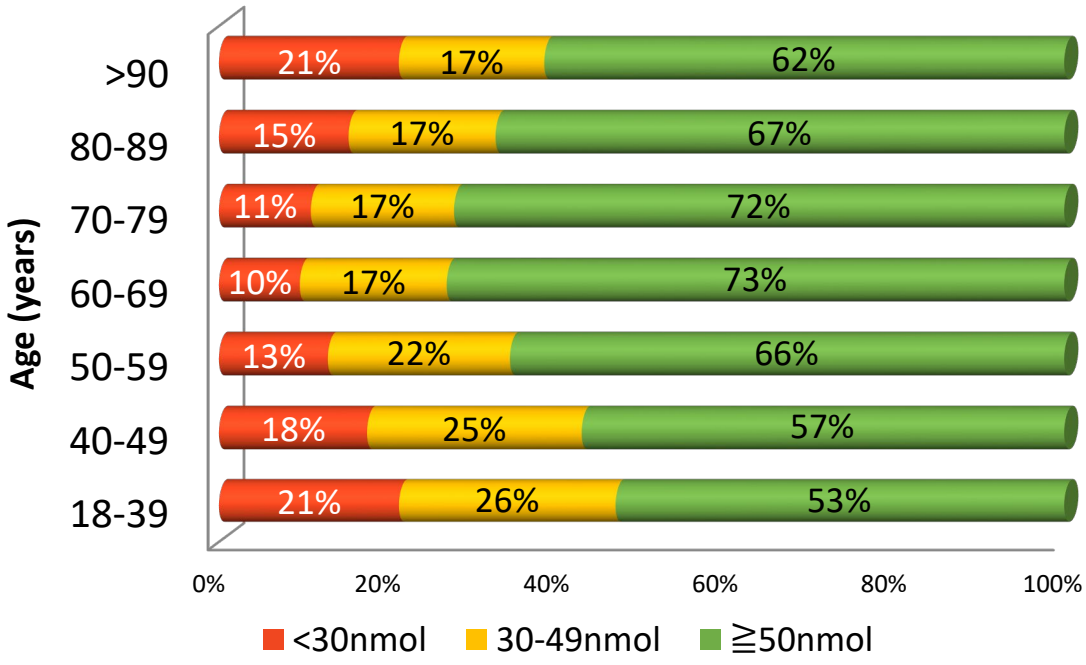


Figure 3.2 25(OH)D Status in Different Age Categories

Table 3.2 25(OH)D Categorised by Year, Age, and Sex

Year	N	Total (%)			Age							Sex						
					<50 years (%)			>50 years (%)			*P*-value	Female (%)			Male (%)			*P*-value
		<30	30-49	>125	<30	30-49	>125	<30	30-49	>125		<30	30-49	>125	<30	30-49	>125	
2014	5394	13	21	3	18	25	3	9	18	4	**<0.001**	12	20	3	16	25	2	**<0.001**
2015	6010	17	24	2	22	29	2	12	20	3	**<0.001**	16	23	3	19	29	1	**<0.001**
2016	7625	16	23	3	20	26	2	11	20	4	**<0.001**	15	21	4	18	27	2	**<0.001**
2017	8869	14	23	3	16	26	2	11	18	4	**<0.001**	12	22	3	17	25	2	**<0.001**
2018	8568	15	24	3	17	27	3	12	20	4	**<0.001**	14	23	4	17	28	2	**<0.001**
Total	36466	15	23	3	18	27	2	11	19	4		14	22	3	17	27	2	

Analysed by frequency distribution and cross tabulation. Significant at $P<0.05$ (bold).

3.3.3 25(OH)D Status by Area - Effect of Season.

The prevalence of deficiency and insufficiency is shown for each area and categorised by season (Table 3.3). Deficiency was greatest in winter at 23%, with a further 26% insufficient. In contrast, deficiency was lowest in summer at 8%, with an additional 16% insufficient. The locations with the lowest 25(OH)D were; Dublin 1 (45.5 ± 31.4 nmol/L), Dublin 11 (46.1 ± 27.3 nmol/L), Lucan (46.5 ± 30.8 nmol/L) and Dublin 8 (49.1 ± 31.9 nmol/L). The locations with the highest 25(OH)D were Dublin 14/16 (59.9 ± 30.8 nmol/L), Dublin 4 (58.8, ± 33.0 nmol/L), Dublin 6/6W (58.6, ± 31.1 nmol/L).

In winter, most locations had a prevalence of deficiency of 20% or more. In particular, in this season the areas (D1, D2, D7, D10, D11, Lucan, North Co. Dublin) and Co. Wicklow had more than 30% who were deficient. A select number of locations (D4, D6, D6W, D14/D16, North Kildare) had a deficiency of 11-20% in winter while no areas had a prevalence of less than 10%. In summer, some areas had no deficiency (Co. Wicklow/ Dublin 9) while in others such as Dublin 5 the prevalence was as high as 16%.

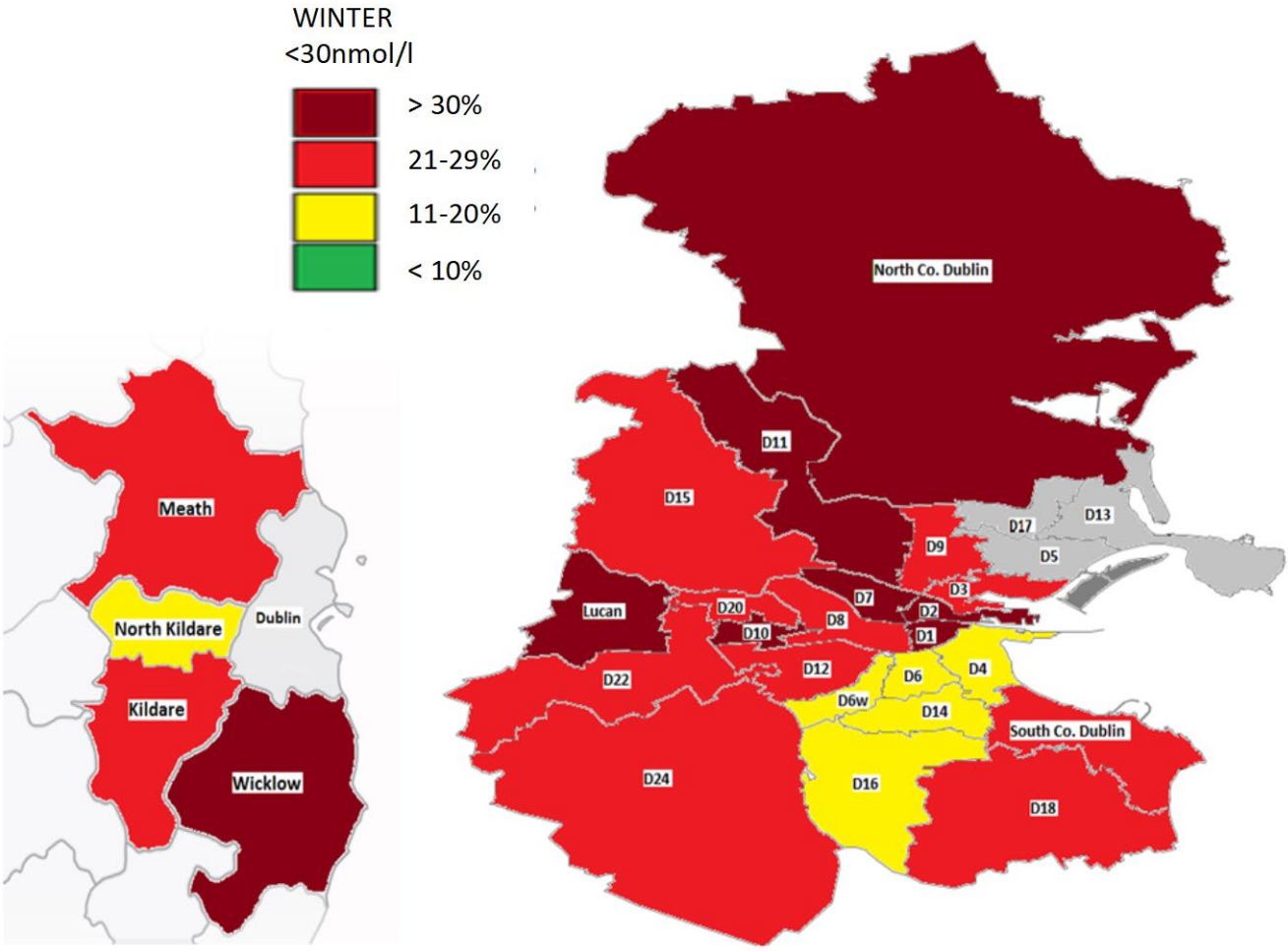
A geomap gives a visual representation of the prevalence of deficiency by location in the summer and winter (Figure 3.3A and 3.3B). This highlights a widespread deficiency in Dublin (20-30%+) and surrounding counties in the winter (Figure 3.3A). However, the opposite is true in the summer where most areas have a prevalence of deficiency less than 10% (Figure 3.3B).

Table 3.3 25(OH)D Status by Area and Season

			Winter			Spring			Summer			Autumn		
General Area	**N**	**GM Mean (SD)**	**n**	**<30**	**30-49**	**n**	**<30**	**30-49**	**n**	**<30**	**30-49**	**n**	**<30**	**30-49**
Dublin 1	290	45.5 (31.4)	76	37	25	88	26	28	66	9	14	60	30	13
Dublin 2	639	49.5 (29.6)	157	34	20	170	21	29	151	9	25	161	19	22
Dublin 3	219	54.9 (33.5)	52	27	23	61	15	21	50	2	22	56	11	38
Dublin 4	662	58.8 (33.0)	132	19	23	181	21	23	169	7	13	180	10	15
Dublin 5	111	54.6 (30.7)	26	8	42	35	17	31	25	16	12	25	12	16
Dublin 6/6W	5273	58.6 (31.1)	1093	19	25	1488	17	22	1256	6	15	1436	8	17
Dublin 7	496	51.4 (31.5)	88	34	27	133	23	27	150	14	12	125	10	22
Dublin 8	2915	49.1 (31.9)	661	28	25	780	27	26	727	12	20	747	17	24
Dublin 9	173	51.0 (29.5)	49	24	29	41	22	32	41	0	22	42	14	21
Dublin 10	846	50.8 (30.5)	173	32	26	210	24	27	235	8	21	228	11	19
Dublin 11	142	46.2 (27.3)	33	39	39	39	18	41	41	12	20	29	17	17
Dublin 12	3375	54.1 (31.8)	734	22	24	1018	22	24	814	9	15	809	12	17
Dublin 13/17	107	52.0 (35.9)	26	23	27	34	24	35	23	4	22	24	17	13
Dublin 14/16	4129	59.9 (30.8)	924	18	23	1181	13	26	963	6	12	1061	8	16
Dublin 15	480	50.3 (31.5)	111	23	28	129	26	29	126	13	20	114	17	17
Dublin 18	372	54.0 (36.9)	84	21	30	106	25	27	75	7	19	107	6	21
Dublin 20	1353	54.3 (29.8)	335	24	25	384	15	28	319	7	20	315	13	21
Dublin 22	719	49.8 (29.5)	129	28	32	218	24	26	202	11	19	170	18	25
Dublin 24	750	52.3 (30.1)	157	25	30	210	24	24	190	10	12	193	12	21
North Co. Dublin	220	50.7 (27.7)	44	36	39	66	18	23	64	5	25	46	13	20
South Co. Dublin	616	55.9 (29.7)	133	23	26	175	13	29	158	6	17	150	12	18
Lucan, Co. Dublin	5008	46.5 (30.8)	1112	32	27	1353	28	28	1204	15	20	1339	18	22
North Co. Kildare	5734	56.1 (27.5)	1329	18	30	1712	18	26	1249	4	15	1444	6	20
Rest of Kildare	757	56.5 (29.0)	170	23	27	215	14	27	166	4	16	206	9	19
Co. Meath	502	56.2 (31.3)	132	22	25	141	19	23	104	5	14	125	6	25
Co. Wicklow	164	58.2 (28.8)	36	33	19	36	11	19	40	0	8	52	10	21
Rest of Leinster	209	54.1 (29.9)	52	27	29	66	17	36	49	6	14	42	2	19

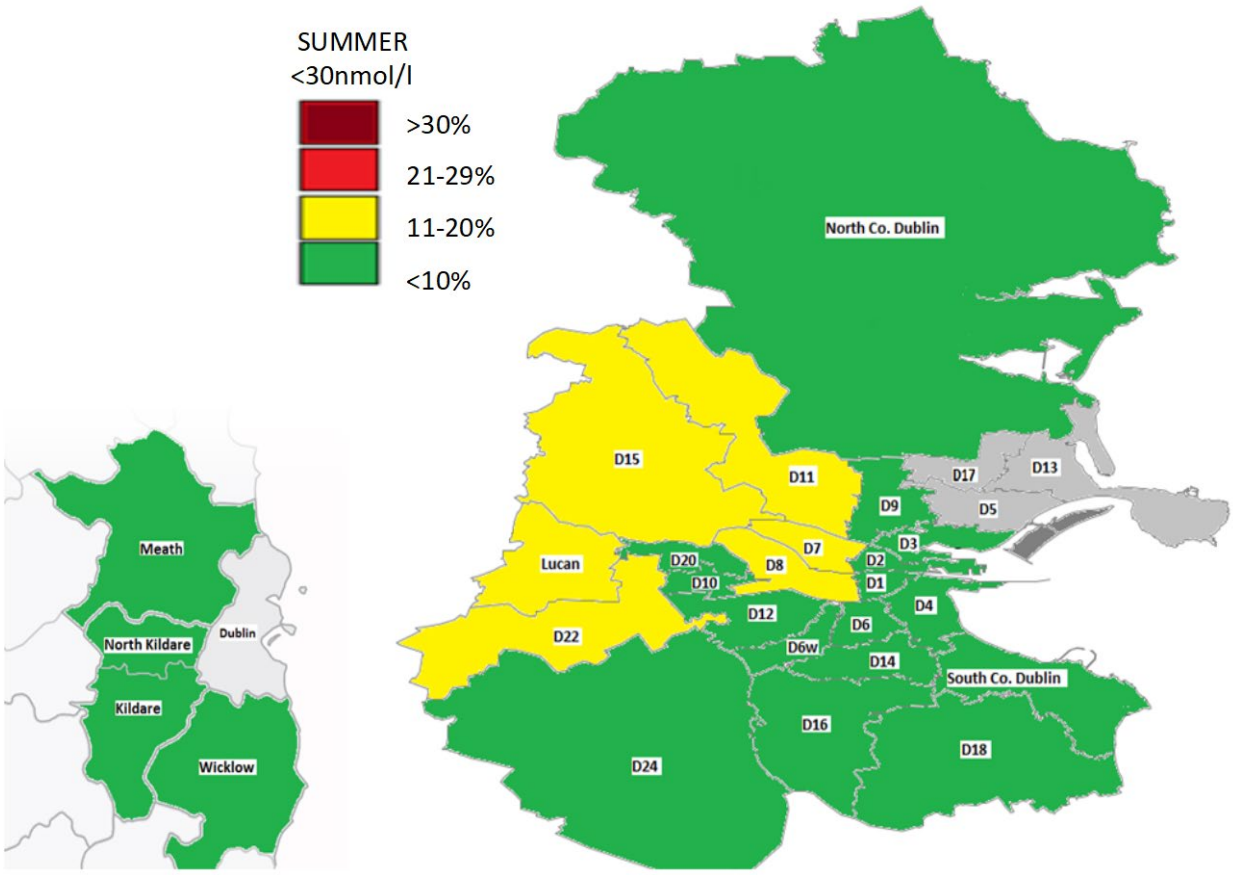
Table 3.3 25(OH)D Status by Area and Season Continued

			Winter			Spring			Summer			Autumn		
General Area	**N**	**GM Mean (SD)**	**n**	**<30**	**30-49**	**n**	**<30**	**30-49**	**n**	**<30**	**30-49**	**n**	**<30**	**30-49**
Rest of Ireland	205	53.8 (30.5)	53	25	28	51	16	29	34	9	18	67	10	24
Total	36466	53.8 (30.8)	8101	23	26	10321	20	26	8691	8	16	9353	11	20



(Areas with insufficient numbers (n<120) for analysis are shown in dark grey)

Figure 3.3A Geomap of 25(OH)D Status in Dublin and Surrounding Counties in Winter.



(Areas with insufficient numbers (n<120) for analysis are shown in dark grey)

Figure 3.3B Geomap of 25(OH)D Status in Dublin and Surrounding Counties in Summer.

3.3.4 25(OH)D Status by Area - Age and Sex

There were significant differences in 25(OH)D status when dichotomised by age across the areas (Table 3.4). In every area, deficiency was more prevalent in those who were younger (<50 years), with this being more marked in some locations. For example, in Lucan, Dublin 1, Dublin 8 and Dublin 22, more than 20% of those aged <50 were deficient. Similarly, in the same areas and also in Dublin 11 more than 50% of this age group had a level below 50 nmol/L. Conversely, in those aged ≥50 only two areas, Dublin 13/17, and Dublin 2, had a level of deficiency and insufficiency above 20%. In just over half of the locations, males were more likely to be deficient, in keeping with the overall study findings. The prevalence of 25(OH)D >125 nmol/L ranged from 1-7% in females, to 0-4% in males and was greatest (7%) in women living in Dublin 3.

Table 3.4 25(OH)D Status by Location, Age, and Sex

	Age							Sex						
	<50 years			>50 years				Female			Male			
General Area	<30	30-49	>125	<30	30-49	>125	*P*-value	<30	30-49	>125	<30	30-49	>125	*P*-value
Dublin 1	26	21	2	17	28	6	0.420	22	22	3	32	23	1	0.547
Dublin 2	17	27	3	22	25	2	0.140	17	28	3	21	23	2	0.611
Dublin 3	14	30	6	4	21	6	**0.025**	11	23	7	14	45	2	**0.009**
Dublin 4	14	21	3	12	16	6	**0.036**	12	17	5	16	25	3	**0.004**
Dublin 5	11	29	4	18	21	0	**0.046**	9	24	4	23	38	0	0.555
Dublin 6/6W	15	24	3	9	18	4	**<0.001**	11	19	5	15	26	2	**<0.001**
Dublin 7	18	26	4	12	13	4	0.672	16	23	5	19	24	2	**0.001**
Dublin 8	23	27	2	14	21	4	**0.002**	19	24	3	24	27	2	**<0.001**
Dublin 9	14	26	5	10	35	0	0.466	12	26	4	17	36	0	0.549
Dublin 10	18	24	3	16	24	2	0.291	16	23	3	20	26	2	0.349
Dublin 11	19	34	2	15	20	5	0.994	18	33	2	19	31	3	0.211
Dublin 12	18	26	2	14	18	3	**<0.001**	15	20	3	18	26	1	**<0.001**
Dublin 13/17	16	26	6	26	21	0	0.962	18	27	5	17	21	4	0.645
Dublin 14/16	13	26	2	9	17	5	**<0.001**	10	18	5	12	25	1	**<0.001**
Dublin 15	20	29	3	10	16	3	0.656	17	25	4	18	28	1	**0.001**
Dublin 18	16	25	3	10	23	6	0.068	14	20	4	16	32	4	**0.042**
Dublin 20	16	28	2	13	23	3	**<0.001**	14	23	4	14	28	1	**<0.001**
Dublin 22	23	28	2	13	23	4	**0.005**	18	22	3	20	34	2	**<0.001**
Dublin 24	22	26	2	9	17	2	**0.004**	15	21	2	21	27	3	**<0.001**
North Co. Dublin	17	26	2	10	32	0	0.215	17	26	1	9	30	4	0.214
South Co. Dublin	13	27	1	10	19	4	0.254	10	25	3	17	22	2	**0.021**
Lucan, Co. Dublin	27	28	2	12	21	3	**<0.001**	21	24	2	25	28	1	**<0.001**
North Co. Kildare	14	28	2	8	20	3	**<0.001**	10	23	2	12	26	2	**<0.001**
Rest of Kildare	16	25	3	8	21	3	0.303	12	22	3	11	26	2	**<0.001**
Co. Meath	14	27	3	8	17	3	0.328	11	24	3	17	22	2	**0.009**
Co. Wicklow	16	18	2	6	19	3	0.329	9	20	2	19	15	4	0.350
Rest of Leinster	16	28	1	7	25	4	0.521	13	25	3	14	32	0	0.167
Rest of Ireland	14	30	4	9	20	4	0.052	10	28	5	20	28	3	0.425
Total	18	27	2	11	19	4		14	22	3	17	27	2	

Notes: Vitamin D categories expressed as % for <30 nmol/L, 30-49 nmol/L, >125 nmol/L, P-value significant at <0.05 (bold)

3.3.5 Determinants of Vitamin D Deficiency and Sufficiency

The independent effects of sex, season, and location on 25(OH)D status are outlined in Table 3.5. Season was the strongest predictor of deficiency followed by geographical area and then sex. Those sampled in the winter versus the summer were over four times more likely to be deficient (OR 4.43, *P*<0.001). In terms of location, those living in North Dublin versus outside Dublin were more likely to be deficient (OR 1.54, *P*<0.001) and insufficient (OR 1.089, *P*<0.001) while those in West Dublin were more than twice as likely to be deficient (OR 2.17, *P*<0.001). We also identified that females were 32% less likely to be deficient (OR 0.68, *P*<0.001).

Table 3.5 Predictors of Vitamin D Deficiency (<30 nmol/L) and Insufficiency (30-49 nmol/L) in Multinomial Regression

Outcome							
Deficient vs. Sufficient	**n**	**B (SE)**	**OR**	**Lower**	**Upper**	**Effect (%)**	***P*-value**
Intercept		1.224 (0.072)					
Age	36,466	0.023 (0.001)	0.977	0.976	0.979	-2	**<0.001**
Female	26,161	0.39 (0.033)	0.677	0.634	0.723	-32	**<0.001**
Winter	8101	-1.49 (0.049)	4.435	4.030	4.881	344	**<0.001**
Spring	10321	-1.275 (0.048)	3.58	3.261	3.930	258	**<0.001**
Autumn	8691	-0.418 (0.052)	1.519	1.372	1.681	52	**<0.001**
North Dublin	1758	-0.431 (0.076)	1.539	1.327	1.786	54	**<0.001**
South Dublin	18827	-0.35 (0.043)	1.419	1.304	1.543	42	**<0.001**
West Dublin	8310	-0.776 (0.047)	2.172	1.981	2.382	117	**<0.001**
Outside Dublin	7571						
Insufficient vs. Sufficient							
Intercept		0.479 (0.058)					
Age	36,466	0.017 (0.001)	0.983	0.982	0.985	-2	**<0.001**
Female	26,131	0.387 (0.029)	0.679	0.642	0.719	-32	**<0.001**
Winter	8101	-0.888 (0.04)	2.430	2.247	2.628	143	**<0.001**
Spring	10321	-0.807 (0.038)	2.241	2.081	2.414	124	**<0.001**
Autumn	8691	-0.264 (0.04)	1.303	1.205	1.408	30	**<0.001**
North Dublin	1758	-0.085 (0.066)	1.089	0.957	1.239	9	**<0.001**
South Dublin	18827	-0.019 (0.034)	1.019	0.953	1.089	2	0.194
West Dublin	8310	-0.256 (0.039)	1.291	1.195	1.395	29	0.586
Outside Dublin	7571						

3.3.6 25(OH)D Status versus Season, Dichotomised by Age and Sex

The seasonality of 25(OH)D is shown in Figure 3.4A where the geometric mean for each season over 5 years is illustrated. Seasonality was similar regardless of age or sex. However, 25(OH)D is consistently higher for those over 50 (mean difference +10.9 nmol/L) and females (mean difference +5.5 nmol/L) across all seasons (Figure 3.4B & 3.4C)

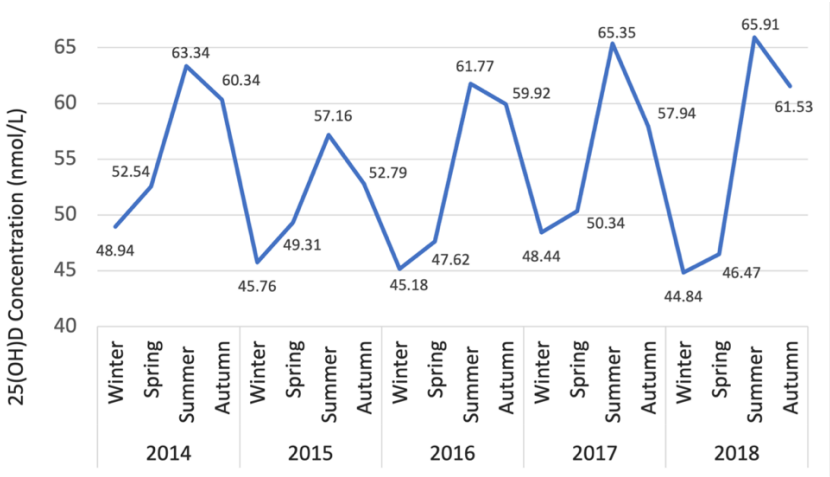


Figure 3.4A 25(OH)D Status Versus Season

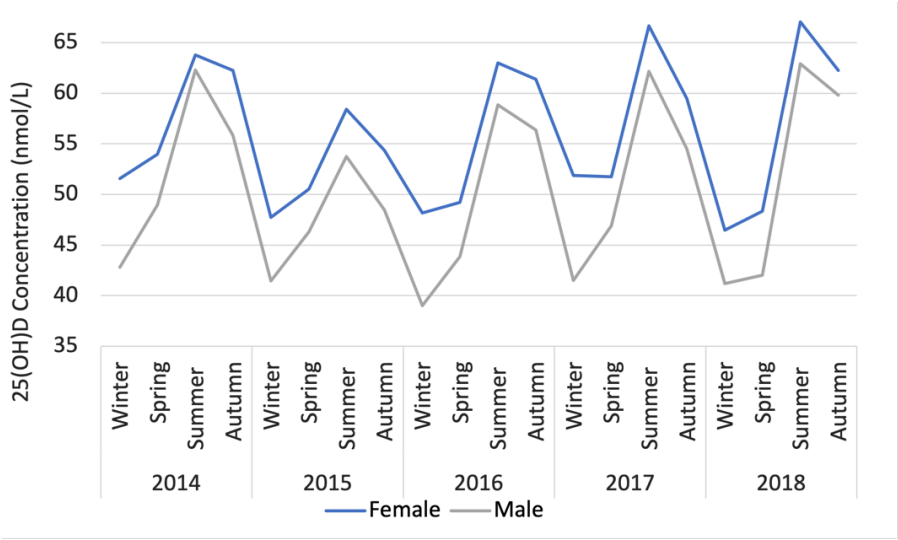


Figure 3.4B 25(OH)D Status Versus Season, Dichotomised by Sex

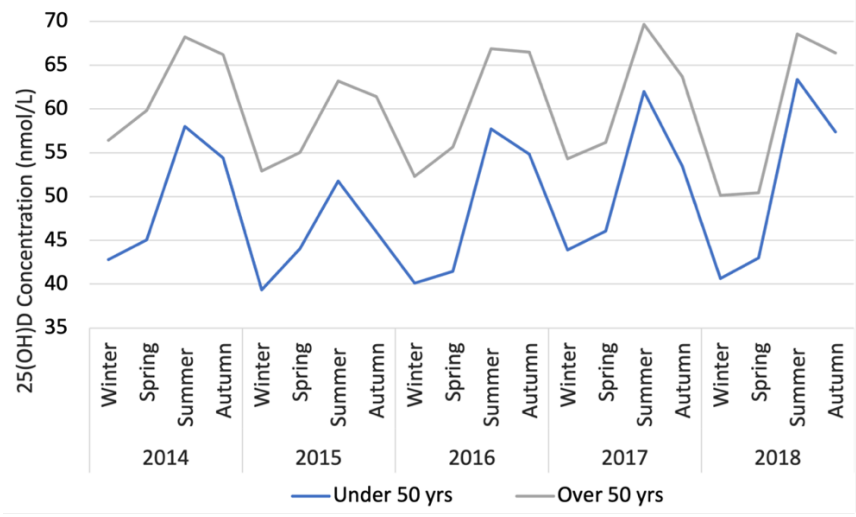
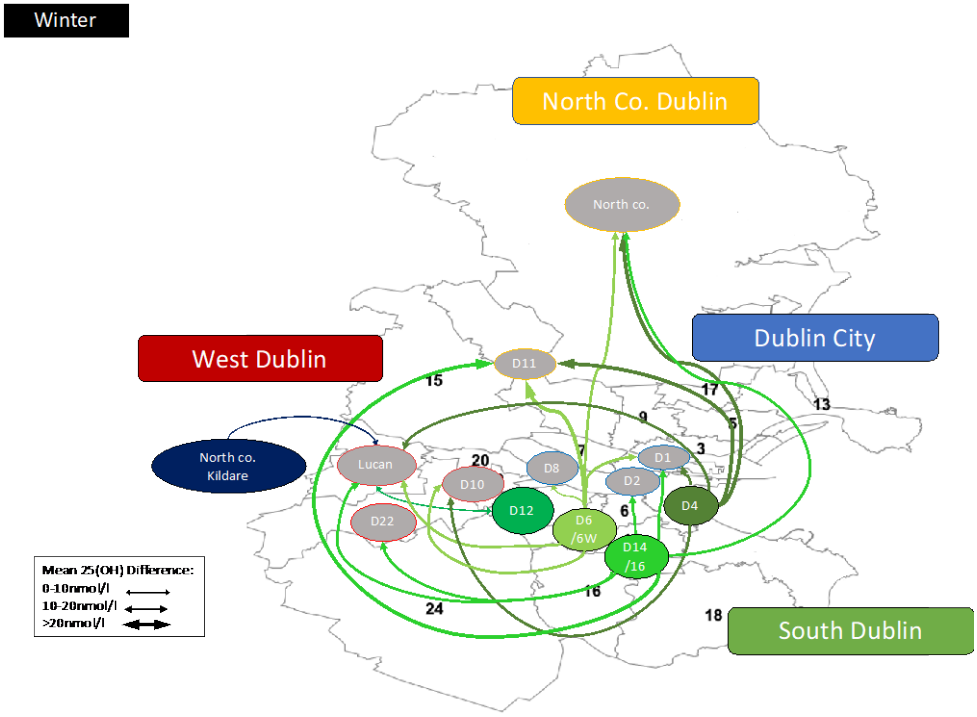


Figure 3.4C 25(OH)D Status Versus Season, Dichotomised by Age

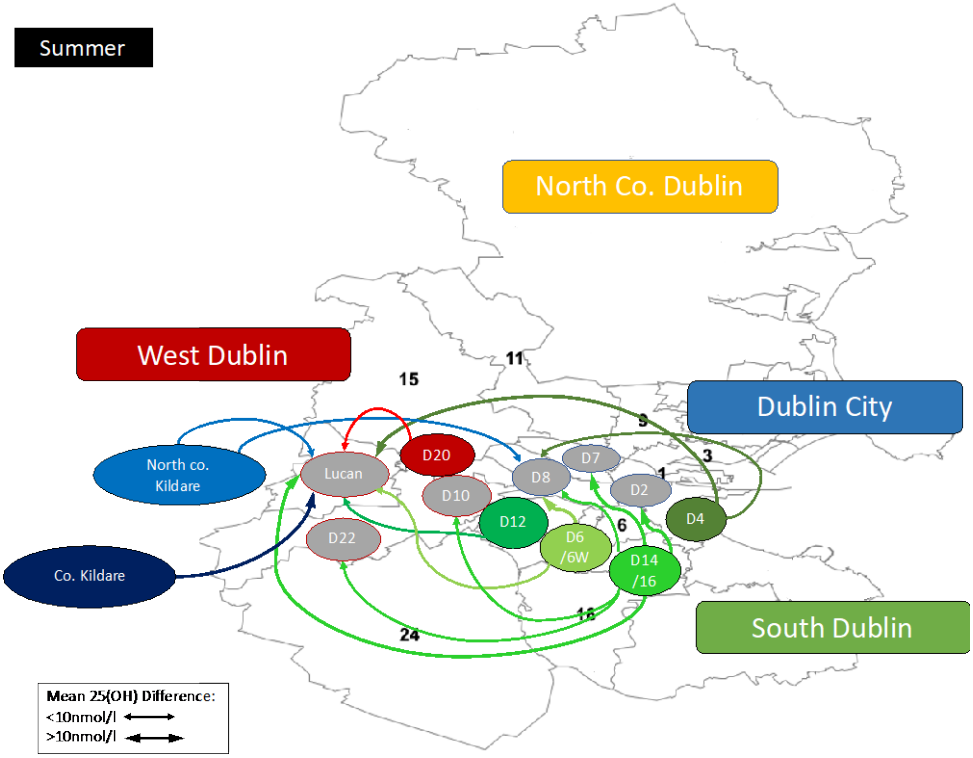
3.3.7 Cluster Analysis of Differences in 25(OH)D Between Areas

Cluster maps of postcodes with significant mean differences in 25(OH)D in the winter (Figure 3.5) and summer (Figure 3.6) were created. There were more areas with significant mean differences in the winter (Table 3.6) than summer (Table 3.7). In winter, higher mean 25(OH)D were identified in the areas (D4, D6/6W, D14/16) with significantly lower levels in central (D1, D2, D8), West (D10, D22, Lucan) and North Dublin (North Co. Dublin, D11). In summer, the areas (D4, D6/6W, D14/16) had higher status versus Dublin city and West Dublin. Finally, North Kildare had a higher 25(OH)D in the summer compared with the areas of Lucan and Dublin 8 and this also remained the case versus Lucan in the winter.



Areas with significant mean differences illustrated using coloured arrows for each area (going in the direction of higher to lower status) and with arrow size representing the size of this difference.)

Figure 3.5 Cluster Map Analysis in Winter.



(Areas with significant mean differences illustrated using coloured arrows for each area (going in the direction of higher to lower status) and with arrow size representing the size of this difference.)

Figure 3.6 Cluster Map Analysis in Summer

Table 3.6 Pairwise ANOVA Winter

General Area	General Area	Mean (SE)	Sig.	95% Confidence Interval	
				Lower	Upper
Dublin 1	Dublin 4	-19.3 (4.3)	0.003	-35.7	-2.8
	Dublin 6/6W	-15.6 (3.6)	0.004	-29.2	-2.0
	Dublin 14/16	-17.2 (3.6)	0.001	-30.8	-3.5
Dublin 2	Dublin 14/16	-10.8 (2.6)	0.011	-20.7	-0.9
Dublin 4	Dublin 1	19.3 (4.3)	0.003	2.7	35.7
	Dublin 10	15.1 (3.5)	0.006	1.8	28.3
	Dublin 11	25.9 (5.8)	0.004	3.6	48.2
	North Co. Dublin	21.8 (5.2)	0.011	1.8	41.7
	Lucan, Co. Dublin	13.9 (2.7)	<0.001	3.4	24.5
Dublin 6/6W	Dublin 1	15.6 (3.6)	0.004	2.0	29.2
	Dublin 8	6.5 (1.5)	0.004	0.9	12.2
	Dublin 10	11.4 (2.5)	0.001	2.0	20.9
	Dublin 11	22.3 (5.3)	0.010	2.0	42.5
	North Co. Dublin	18.2 (4.6)	0.031	0.5	35.8
	Lucan, Co. Dublin	10.3 (1.3)	<0.001	5.5	15.2
Dublin 8	Dublin 6/6W	-6.5 (1.5)	0.004	-12.2	-0.9
	Dublin 14/16	-8.0 (1.5)	<0.001	-13.9	-2.2
Dublin 10	Dublin 4	-15.0 (3.5)	0.006	-28.3	-1.8
	Dublin 6/6W	-11.4 (2.5)	0.001	-20.8	-2.0
	Dublin 14/16	-12.9 (2.5)	<0.001	-22.4	-3.4
Dublin 11	Dublin 4	-25.9 (5.8)	0.004	-48.2	-3.6
	Dublin 6/6W	-22.3 (5.3)	0.010	-42.5	-2.0
	Dublin 14/16	-23.8 (5.3)	0.003	-44.1	-3.5
Dublin 12	Lucan, Co. Dublin	7.3 (1.4)	<0.001	1.8	12.7
Dublin 14/16	Dublin 1	17.2 (3.6)	0.001	3.5	30.8
	Dublin 2	10.8 (2.6)	0.011	0.9	20.7
	Dublin 8	8.0 (1.5)	<0.001	2.2	13.9
	Dublin 10	12.9 (2.5)	<0.001	3.4	22.4
	Dublin 11	23.8 (5.3)	0.003	3.5	44.0
	Dublin 22	11.7 (2.8)	0.012	0.9	22.5
	North Co. Dublin	19.7 (4.6)	0.008	2.0	3.4
	Lucan, Co. Dublin	11.9 (1.3)	<0.001	68	17.0
Dublin 22	Dublin 14/16	-11.7 (2.8)	0.012	-22.5	-0.9
North Co. Dublin	Dublin 4	-21.8 (5.2)	0.011	-41.7	-1.8
	Dublin 6/6W	-18.2 (4.6)	0.031	-35.8	-0.5
	Dublin 14/16	-19.7 (4.6)	0.008	-37.4	-2.0
Lucan, Co. Dublin	Dublin 4	-14.9 (2.8)	<0.001	-24.5	-3.4
	Dublin 6/6W	-10.3 (1.3)	<0.001	-15.2	-5.5
	Dublin 12	-7.3 (1.4)	<0.001	-12.7	-1.8
	Dublin 14/16	-11.87 (1.3)	<0.001	-17.0	-6.8
	North Co. Kildare	-7.4 (1.2)	<0.001	-12.0	-2.7
North Co. Kildare	Lucan, Co. Dublin	7.4 (1.2)	<0.001	2.7	12.1

Table 3.7 Pairwise ANOVA Summer

General Area	General Area	Mean (SE)	Sig.	95% Confidence Interval	
				Lower	Upper
Dublin 2	Dublin 14/16	-12.0 (2.6)	0.001	-21.7	-2.2
Dublin 4	Dublin 8	9.8 (2.5)	0.033	0.3	19.3
	Lucan, Co. Dublin	13.2 (2.4)	<0.001	4.0	22.3
Dublin 6/6W	Dublin 8	6.1 (1.4)	0.003	0.93	11.3
	Lucan, Co. Dublin	9.5 (1.1)	<0.001	5.0	14
Dublin 7	Dublin 14/16	-11.0 (2.6)	0.006	-20.8	-1.2
Dublin 8	Dublin 4	-9.8 (2.5)	0.033	-19.3	-0.3
	Dublin 6/6W	-6.1 (1.4)	0.003	-11.3	-0.9
	Dublin 14/16	-10.1 (1.4)	<0.001	-15.6	-4.6
	North Co. Kildare	-6.4 (1.4)	0.001	-11.6	-1.2
Dublin 10	Dublin 14/16	-8.1 (2.1)	0.046	-16.2	-0.0
Dublin 12	Lucan, Co. Dublin	9.0 (1.3)	<0.001	3.9	14.0
Dublin 14/16	Dublin 2	12.0 (2.6)	0.001	2.2	21.7
	Dublin 7	11 (2.56)	0.006	1.2	20.8
	Dublin 8	10.1(1.4)	<0.001	4.6	15.5
	Dublin 10	8.1 (2.1)	0.046	0.04	16.2
	Dublin 22	9.4 (2.3)	0.013	0.7	18.0
	Lucan, Co. Dublin	13.4 (1.3)	<0.001	8.7	18.3
Dublin 20	Lucan, Co. Dublin	8.6 (1.8)	0.001	1.5	15.6
Dublin 22	Dublin 14/16	-9.4 (2.3)	0.013	-17.8	-0.7
Lucan, Co. Dublin	Dublin 4	-13.2 (2.4)	<0.001	-22.3	-4.0
	Dublin 6/6W	-9.5 (1.2)	<0.001	-14	-5.0
	Dublin 12	-9.0 (1.3)	<0.001	-14.0	-3.9
	Dublin 14/16	-13.5 (1.3)	<0.001	-18.3	-8.7
	Dublin 20	-8.6 (1.8)	0.001	-15.6	-1.5
	North Co. Kildare	-9.8 (1.2)	<0.001	-14.3	-5.3
	Rest of Kildare	-10.9 (2.4)	0.002	-20.1	-1.7
North Co. Kildare	Dublin 8	6.4 (1.4)	0.001	1.2	11.6
	Lucan, Co. Dublin	9.8 (1.2)	<0.001	5.3	14.3
Rest of Kildare	Lucan, Co. Dublin	10.9 (2.4)	0.002	1.7	20.1

3.4 Discussion

To our knowledge this is the largest geomapping study of vitamin D status in Europe. We observed that nearly one in six (15%) of a GP Primary Care tested population in Dublin and surrounding areas were vitamin D deficient, rising to one in four (23%) in the winter. Furthermore, an additional 26% were insufficient (30-49 nmol/L), with nearly half of those tested having 25(OH)D levels <50 nmol/L in the winter. We also identified major differences in the prevalence of deficiency between Dublin postal code areas, despite being in close proximity to each other, as well as in other counties. This is concerning as it suggests that a significant proportion of Dublin and surrounding area population have inadequate 25(OH)D status.

3.4.1 Vitamin D Status by Sex

We observed that overall, females had higher vitamin D serum levels across all age groups, similar to other studies [48, 56, 156]. In fact, females were about a third (32%) less likely to be deficient. Some research conflicts with this [338, 339] although a meta-analysis of 394 studies (n=33,266) discovered higher mean 25(OH)D in women, with levels comparable to our study [340]. In about half of locations the difference in 25(OH)D between sex was not statistically significant, but the analysis may have been underpowered due to smaller sample sizes in some areas. In addition, other factors related to sex which we were not able to adjust for might account for this.

The majority of vitamin D requests (72%) were for females, a finding which has been reported elsewhere [25, 156]. Females may be more likely to attend their GP and partake in positive health behaviours [341]. They are also more likely to take a dietary supplement [342]. For example, in one study, females (particularly those aged over 50) were more than twice as likely to routinely take a vitamin supplement [67, 68]. Furthermore, there is a greater awareness of the importance of bone health in women, where osteoporosis is more prevalent and emphasis is placed on prevention and treatment [69].

3.4.2 Vitamin D Status by Age

Those who were younger (<50 years) had lower vitamin D status. This did not change over the 5-year period, with about 1 in 5 of those aged <50 being deficient compared to 1 in 10 over 50. Surprisingly, those aged between 18-39 years had the same prevalence of deficiency (21%) as the oldest age group (+90 years). This nadir in 25(OH)D in young adults was also found in the similarly located northern latitude (51°N) city of Calgary, Alberta [270]. A 'U'-shaped distribution of vitamin

D deficiency in the youngest and oldest adults has likewise been described in the West of Ireland [156], Romania [269], and São Paulo, Brazil [272].

One reason why younger adults may be deficient is that they may spend more time indoors e.g., in their working environment. A study by Sowah et al., 2017 found that shift workers, healthcare and indoor workers have a higher risk of deficiency due to a lack of opportunity for sunshine exposure [273]. Another factor in younger adults may be the difference in dietary intake of vitamin D. In a recent Irish dietary survey, it was estimated that 19.2% of the population are now vegan, vegetarian, or seeking to reduce dietary animal products with the majority of those being younger (aged 18-34) [330]. This may be a cause for concern as meat is the largest contributor of vitamin D in adults under 65, accounting for a third of total dietary intake [94]. Moreover, when compared to those over 65, the proportion of adults who did not meet the recommended dietary intake at that time (5 μg/day) was greater in the age group (18-64) for both males (72% vs. 59%) and females (78% vs 58%) [94].

Ensuring adequate vitamin D status in younger adults is important as peak bone mass is acquired in the early to late twenties [343]. Suboptimal 25(OH)D earlier in life and over prolonged periods might also contribute to other adverse health outcomes as consistent with the theory of 'long latency deficiency disease' [344]. For example, vitamin D deficiency has been associated with up-regulation of inflammatory markers, endothelial dysfunction and chronic low-grade inflammation that may increase the risk of cardiovascular disease as well as mortality from cancer and other causes [345, 346].

Our findings demonstrate that 25(OH)D peaked in the decade (60-69 years) in which most people retire and may reflect more time spent outdoors [43]. Conversely, 25(OH)D levels declined from the age of 70 onwards. This may largely relate to increasing frailty and less sunshine exposure. However, reduction in the capacity of the skin to synthesize vitamin D by up to 75% with age may also help to explain this [347]. In addition, sequestration of vitamin D within increased body fat with ageing as well as reduced dietary intake may contribute [61]. Furthermore, poor compliance with vitamin D supplements in older adults, especially in those where there is polypharmacy may also be a factor [348].

3.4.3 Vitamin D Status by Season and Location

A geomap depicting 25(OH)D status in Dublin and the surrounding areas illustrates major variations in the prevalence of deficiency by location. This varied greatly especially in the winter, where it ranged from 18% in areas like Dublin 14/16 and North Co. Kildare to up to 37%+ in Dublin 1 and Dublin 11. Findings were similar to a previous geomapping study of vitamin D status in Dublin, although that study focused on a substantially smaller population, did not include as many areas, and only covered a one-year period [25].

In the winter, we found clusters of areas South Dublin (D4, D6/6W, D14/16) with greater serum 25(OH)D compared to West Dublin, North Dublin, and more central Dublin city areas. In fact, these particular locations in South Dublin are some of the most affluent areas in the county and nationally, as determined by HP Pobal Score 2016, a deprivation index of Demographic Profile, Social Class Composition and Labour Market Situation [349]. Socioeconomic status and 25(OH)D have been closely linked, with those in typically disadvantaged areas having an increased risk of deficiency [270, 350]. For example, in the TILDA study of Irish adults, those with lower asset wealth were 1.5 times more likely to be deficient. This may be due to factors linked to lower socioeconomic status including reduced dietary vitamin D intake, less sun holiday travel and possibly higher rates of obesity and smoking [48, 106].

In the summer, most areas had a prevalence of deficiency of less than 10% except locations such as North and West Dublin including Lucan. This may be in part accounted for by a greater proportion of individuals of Asian and Black ethnicity living here [351]. Indeed, those with darker or more pigmented skin have a greater risk of deficiency at locations in northern latitudes [340]. However, overall season had a large impact on 25(OH)D in keeping with those in the winter being over four times more likely to be deficient versus in the summer [352, 353]. Importantly, the extent of the differences in deficiency between areas appeared to be attenuated in the summer, highlighting the importance of sun exposure.

Those living in the areas of North and West Dublin were also more likely to be deficient compared to those living outside Dublin. While we did not define rural or urban areas, locations outside Dublin are less urbanised and some are rural. These findings contrast with a study by Griffin et al., 2019, which found that Irish urban dwellers had higher 25(OH)D and lower rates of deficiency [156]. However, these differences might be accounted for by local variations in socioeconomic status and ethnicity.

There was no improvement in vitamin D status over a five-year period despite increased testing and greater awareness [332]. This suggests that a large proportion of the population have inadequate 25(OH)D but have not yet been identified. As the list of potential co-morbidities related to vitamin D expands beyond bone and muscle health, it is important that no sub-group of the population are left vulnerable to deficiency. For example, vitamin D may help to maintain immune function, reduce the risk of respiratory infections, and downregulate inflammatory cytokines, suggesting that deficiency could have a negative impact on Covid-19 outcomes [43, 354].

We did find that a small (1-7%) but not insignificant proportion of our study population had 25(OH)D levels >125 nmol/L, particularly females over 50 who may be more likely to take prescribed or over-the-counter vitamin D. While a similar prevalence (>125 nmol/L) has been identified elsewhere [353], it is important that any future Irish guidance on vitamin D intake, takes into account the potential for inadvertently increasing the risk of hypervitaminosis D. Recent evidence from a large trend analysis indicates that prevalence of concentrations >125 nmol/L was higher in the years 2020-2021 compared to 2017-2019, and was attributed to the increased availability of high-dose supplements [89]. However, no data on serum calcium concentrations was available, thus conclusions on the risk of vitamin D toxicity could not be made. In this investigation, just 2% of those with levels >125 nmol/L had corrected serum calcium greater than 2.5 nmol/L, 0.7% with levels >2.7 nmol/L with the highest level observed 25(OH)D (308 nmol/L) having normocalcaemia.

There are no national Irish guidelines regarding vitamin D testing, and recommendations for supplementation are limited to infants. This study highlights the presence of vulnerable groups with vitamin D deficiency, including males and young adults, living in poorer socioeconomic areas. Furthermore, our geomap and cluster analysis highlights locations where the prevalence of deficiency is significantly higher. These findings provide valuable information for GPs and public health bodies in developing strategies for targeted interventions to optimise vitamin D status.

3.4.4 Strengths of Study

The primary strength of this study was its large population size and the novel use of a geomap to gain a visual representation of vitamin D status in a large city and its surrounding areas. In fact, to our knowledge, this is the largest study in Europe to geomap vitamin D and includes data collected

over a 5-year period. We used the gold standard for vitamin D assessment, LC-MS/MS, NIST internal standard and are DEQAS accredited to ensure accuracy.

3.4.5 Limitations of Study

Our study was based on GP vitamin D requests and this limits the generalisability of the findings to a wider population. In particular, there is likely to be selection bias in testing with study participants having medical conditions or other factors putting them at risk of deficiency. However, unlike other studies we minimised the potential for this by not including vitamin D samples received from outpatient or acute hospital services and excluded those from institutionalised adults.

We were not able to adjust for several factors that influence 25(OH)D including biophysical (BMI, skin type, medical conditions e.g., malabsorption syndromes) and lifestyle (supplementation, smoking, sun exposure, alcohol intake, diet, education). Finally, our study was cross sectional and therefore we could not make any direct inferences as to the causality of factors influencing vitamin D status.

3.5 Conclusion

This study shows that nearly one in four of the GP tested population in Dublin and surrounding areas are vitamin D deficient in the winter, during which time up to 50% have 25(OH)D less than 50 nmol/L. Moreover, those living in poorer socioeconomic areas were more likely to be deficient, as are males, younger (18-39 years) and older adults (80+ years). This study identifies key groups at risk of vitamin D deficiency and provides important public health information for the targeting of interventions to optimise vitamin D status. Our data indicated that inadequate vitamin D status is not just limited to older adults, but it is widespread across many population groups. This highlights the importance for recommendations for vitamin D intake to include the entire population and/or mandatory vitamin D food fortification.

Chapter 4: Vitamin D Retesting by General Practitioners: A Factor and Cost Analysis

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The PDF of this manuscript can be found in Appendix Section C (ii): Thesis-related Publications

4.1 Introduction

In Ireland, there has been a substantial increase in vitamin D testing in the last decade [16], with a 37% rise in requests between 2014 and 2018 [154], consistent with an observed global surge [14]. Testing in the UK has increased fifty-fold between 2005 and 2015 [355]. Varying increases have been identified elsewhere, with a 4-fold increase in Canada [356], 7.5-fold in France [357], and 94-fold in Australia [358] over a similar period. In Denmark, testing rose from 1 in 500 inhabitants in 2004, to 1 in 5 in 2010 [359], while in the US it was a top five most requested test, costing $350 million in 2017 [360]. This increase may be related to greater public awareness and media interest in vitamin D and its potential but unproven benefits beyond bone health [14]. Currently, Ireland is lacking data on the appropriateness of vitamin D testing, including clinical indications and retesting prevalence in primary care.

There are numerous guidelines by various organisations regarding indications for vitamin D testing [30, 361]. Most focus on criteria for initial testing, with different recommendations on when to retest [361-363]. The Royal Osteoporosis Society advises monitoring is generally unnecessary but may be appropriate for symptomatic vitamin D deficiency or malabsorption or where poor compliance is suspected [361]. In the UK, despite recommendations, inappropriate testing accounted for 70-77% of vitamin D tests, with malaise/tiredness contributing between 20-30% of tests [27]. Vitamin D testing by General Practitioners' (GPs) for non-specific conditions such as fatigue has been reported in the Netherlands [364]. In Canada, a quarter of vitamin D tests were repeated too early, with undefined clinical indications in many instances [28]. Furthermore, while women are more likely to be vitamin D sufficient compared with men, they are more likely to be tested [150, 355].

In Ireland, the Health Service Executive (HSE) suggest testing for metabolic bone disorders where vitamin D may improve outcomes such as osteoporosis, hyperparathyroidism, and Paget's disease [26]. It includes other conditions that might lead to or be attributed to deficiency including malabsorption conditions (coeliac/inflammatory bowel disease), unexplained musculoskeletal symptoms, liver disease and for certain medications (e.g., anti-epileptics) [26]. However, screening for otherwise asymptomatic individuals at-risk of deficiency is not recommend. It also advises against routine retesting but provides no specific criteria for who should be retested.

Presently in Ireland data on vitamin D retesting is limited, including its contributary factors and cost implications. In this study, we aim to explore the predictors of vitamin D retesting by primary

care doctors with regard to age, sex, initial status, and GP location. Secondly, we will investigate vitamin D status after retesting, and examine costs due to inappropriate requests.

4.2 Methods Particular to this Chapter

Detailed methods regarding Ethical Approval, Serum 25(OH)D Measurement and Statistical Analysis are outlined in Section 2.1, 2.2 and 2.4, respectively. Methods specific to this study are provided below.

4.2.1 Data Collection

Full details of the data collection procedure are provided in the Methods Section 2.3. In this analysis,

Repeat vitamin D results were identified and coded

4.2.2 Statistical Analysis

Patients were categorised into a baseline cohort (initial vitamin D test but no retests), with retested cohorts divided into; initial test, first retest or ≥2 retests. Determinants of retesting, including age category, sex, geographical area, and sampling season was explored using multi-nominal logistic regression. We defined five areas (North, South and West Dublin, Kildare, and Rest of Ireland) as previously described [154]; with rest of Ireland as the reference area. Seasons were defined as winter: (December, January, February); Spring: (March, April, May); Summer: (June, July, August); Autumn: (September, October, November).

4.2.3 Cost Analysis

Cost analysis estimated the number of patients needed to test (NNT) to detect one with deficiency, insufficiency, or excess vitamin D (>125 nmol/L) by sex, age, and location. The percentage in each vitamin D category was divided into 100 to calculate the NNT. Inappropriate testing costs was estimated, defined as (1) retests within 3 months of the first or initial test, (2) two or more retests within one year and (3) retests in those who were initially vitamin D replete (50-75 nmol/L). The calculation was predicated on a laboratory cost of €40 per 25(OH)D sample.

4.3 Results

4.3.1 Demographics

Over five years, 50,088 serum 25(OH)D tests were reported to GPs after exclusion criteria. There were 36,458 patients in the study, representing 8,305 retested and 28,153 were who were not retested. Baseline demographics of non-retested and retested group are displayed in Table 4.1. In the retested cohort, there were 21,935 samples, including 8,305 initial baseline results, 8,305 first retests and 5,325 ≥2 retests. Overall, 22.8% of patients were retested, accounting for 27.2% of vitamin D requests. Retesting numbers was similar between 2014-2016 but lower in 2017-2018 (Table 4.2).

The retested cohort were more likely to be female (72.4% vs. 71.4%, P=0.047), older (51.6yrs ± 16.3 vs. 46.4yrs ± 17.7, P<0.001) and live in County Kildare (23.2% vs. 16.2%, P<0.001) but less likely to live in South (48.7% vs. 52.5%, P<0.001) or North Dublin (3.0% vs. 5.4%, P<0.001) versus the non-retested. The proportion of young people (<50yrs) that were retested was smaller (42% vs. 55%, P<0.001). Retesting was more prevalent in those age 50-59 years (19.9% vs. 16.6%, P=0.04), 60-69 years (20.8% vs. 14.3%, P<0.001), and 70-79 years (12.9% vs. 9.9%, P<0.001). The percentage of very old adults (<90yrs) was similar between both groups (0.6% vs. 0.4%) albeit the difference statistically significant (P<0.001). There was no difference in the proportion tested in Winter. Vitamin D deficiency at baseline was greater in the retested group (17.8% vs. 13.9%, P<0.001) as was insufficiency (25.3% vs. 24.1%, P=0.022).

Table 4.1 Characteristics of Study Population at Baseline (Non-Retested and Retested)

		Non-retested N= 28,153	Retested N= 8,305	*P*-value
	N	**n (%)**	**n (%)**	
25(OH)D[a]	36458	54.5 (30.2)	51.5 (31.9)	**<0.001**
<30 nmol/L	5401	3917 (13.9)	1484 (17.8)	**<0.001**
30-49.9 nmol/L	8896	6791 (24.1)	2105 (25.3)	**0.022**
>50 nmol/L	22163	17445 (62.0)	4718 (56.8)	**<0.001**
Female	26129	20116 (71.4)	6013 (72.4)	**0.047**
Age (yrs)[a]	36458	46.4 (17.7)	51.6 (16.3)	**<0.001**
Winter sample (%)	14609	11330 (40.2)	3279 (39.5)	0.109
Age Category (yrs)	**N**	**n (%)**	**n (%)**	
Age <50	18962	15482 (55)	3480 (42)	**<0.001**
18-39	11339	9573 (34.0)	1766 (21.3)	**<0.001**
40-49	6978	5428 (19.3)	1550 (18.7)	0.209
50-59	6329	4678 (16.6)	1651 (19.9)	**0.040**
60-69	5750	4021 (14.3)	1729 (20.8)	**<0.001**
70-79	3854	2778 (9.9)	1076 (12.9)	**<0.001**
80-89	1990	1494 (5.3)	496 (5.9)	**0.019**
>90	218	181 (0.6)	37 (0.4)	**<0.001**
Districts	**N**	**n (%)**	**n (%)**	
North Co. Dublin	1758	1512 (5.4)	246 (3.0)	**<0.001**
South Co. Dublin	18817	14771 (52.5)	4046 (48.7)	**<0.001**
West Co. Dublin	8308	6442 (22.9)	1866 (22.5)	0.490
Co. Kildare	6496	4571 (16.2)	1925 (23.2)	**<0.001**
Rest of Ireland	1079	857 (3.0)	222 (2.7)	0.080

[a]Indicates results reported as Geometric Mean (SD). Winter was defined as October-February. Independent sample t-tests for continuous and cross-tabulation with Chi-squared for categorical variables were used. Significant at $P<0.05$ (bold).

Table 4.2 Vitamin D Status of Study Population by Year

		Vitamin D Status (nmol/L)				
Year		**<30**	**30-49**	**50-74**	**75-124**	**>125**
Not Retested (n= 28,153)	**N (%)**	**%**	**%**	**%**	**%**	**%**
2014	3191 (11.3)	13.1	23.2	31.3	29.4	2.9
2015	4053 (14.4)	15.9	25.5	30.3	26	2.3
2016	5614 (19.9)	15.1	22.9	31.1	28	3
2017	7199 (25.6)	12.4	23.7	31.2	29.6	3.2
2018	8096 (28.8)	13.7	25.1	31	26.8	3.3
Retested (n= 8,305)	**N (%)**					
2014	2187 (26.3)	13.4	21.2	30.2	31.9	3.3
2015	1952 (23.5)	18.9	26.9	26.4	25.5	2.4
2016	2017 (24.3)	17.9	27.4	24.3	27.4	3
2017	1669 (20.1)	18.8	25.6	24.6	28.3	2.6
2018[a]	480 (5.8)	30.4	28.5	20.6	18.1	2.3

Analysed by frequency distribution and cross tabulation. [a] Data is based on smaller sample size as follow up period to capture retests was limited.

4.3.2 Predictors of Retesting

The predictors of retesting are shown in Table 4.3. Deficient and insufficient patients were respectively 70% (OR 1.70, CI 1.58-1.83, *P*<0.001) and 28% (OR 1.28, CI 1.21-1.36, *P*<0.001) more likely to be retested. The other main predictor was age, with those between 18-39 years least likely to be retested (OR 0.51, CI 0.47-0.55, *P*<0.001), followed by those aged >90 years (OR 0.60, CI 0.42-0.86, *P*=0.005). Location was also a predictor, with those living in North County Dublin (OR 0.68, CI 0.55-0.83, *P*<0.001) least likely, and those in the Kildare most likely to have a retest (OR 1.46, CI 1.24-1.71, *P*<0.001). Females were 15% more likely to be retested (OR 1.15, CI 1.09-1.21, *P*<0.001) as were those who were initially tested in the Summer (OR 1.06, CI 1.01-1.12, *P*=0.02).

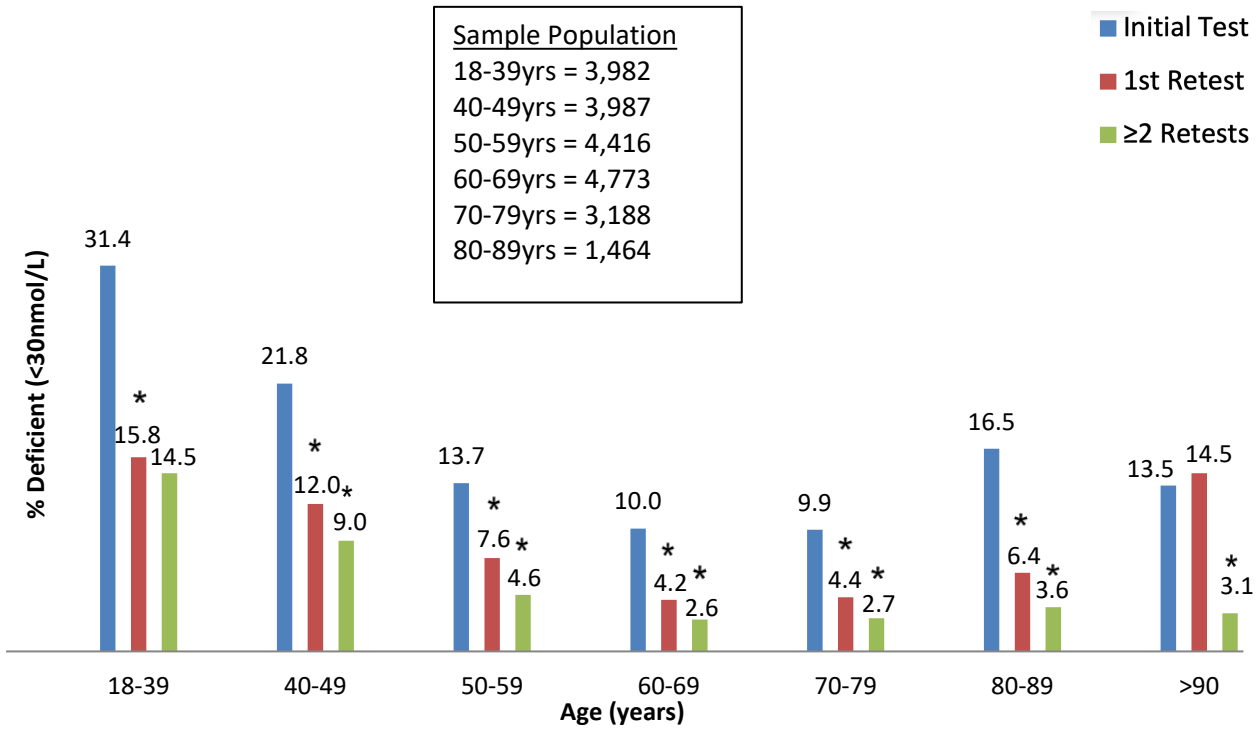
Table 4.3 Predictors of Retesting (On First Retest)

Retested vs. Not Retested	N			Confidence interval		
		B	OR	Lower	Upper	*P*-value
Intercept	36458	-1.34				
Female	26129	0.14	1.15	1.09	1.21	**<0.001**
Age (yrs)						
18-39	11339	-0.68	0.51	0.47	0.55	**<0.001**
40-49	6978	-0.24	0.79	0.73	0.85	**<0.001**
60-69	5750	0.22	1.25	1.15	1.35	**<0.001**
70-79	3854	0.15	1.16	1.06	1.27	**0.001**
80-89	1990	0	1.00	0.89	1.13	0.984
>90	218	-0.51	0.60	0.42	0.86	**0.005**
50-59[a]	6329					
Location						
North Co. Dublin	1758	-0.39	0.68	0.55	0.83	**<0.001**
South Co. Dublin	18817	-0.08	0.92	0.79	1.08	0.310
West Co. Dublin	8308	0.01	1.00	0.86	1.18	0.960
Co. Kildare	6496	0.38	1.46	1.24	1.71	**<0.001**
Rest of Ireland[a]	1079		.	.	.	
Vitamin D (nmol/L)						
<30	5401	0.53	1.70	1.58	1.83	**<0.001**
30-50	8896	0.25	1.28	1.21	1.36	**<0.001**
>50[a]	22161		.	.	.	**.**
Season- Summer	21849	0.06	1.06	1.01	1.12	**0.020**
Winter[a]						

[a]Indicates reference variable, analysed using Multinominal Logistic Regression. Significant at *P*<0.05 (bold).

4.3.3 Vitamin D Status in Retested Population

Over half (57%) of retested patients were initially vitamin D replete (>50 nmol/L), with 26% between 50-74 nmol/L. Baseline deficiency was more prevalent in retested males versus females (20% vs. 17%) (Table 4.4). Mean 25(OH)D increased with each retest, with a larger increment between the initial and first retest (+11.0 nmol/L, *P*<0.001) versus first retest and ≥2 retests (4.7 nmol/L, *P*<0.001). This was identified in both males and females. The increase in mean 25(OH)D on first retest was found in all age groups (*P*<0.001) except those >90 years. The 60-69 years group was the only one with a statistically significant improvement in mean 25(OH)D with ≥2 retests (*P*=0.002). Deficiency was halved on first retest (9% vs. 18%, *P*<0.001) dropping to 6% on further retests. Insufficiency also declined with each retest, irrespective of sex (*P*<0.013). Similarly, deficiency decreased between initial and first retest, and first and ≥2 retests in most age groups (Figure 4.1). There was a substantial decrease in deficiency between 1st and 2nd retest, regardless of season or location (see Figure 4.2 & 4.3). Excess vitamin D (>125 nmol/) were more prevalent (occurring in up to 4-5%) on retesting in both sexes (*P*<0.001).



*Indicates significance (*P*<0.05)

Figure 4.1 Vitamin D Deficiency (<30 nmol/L) on Retest by Age Category

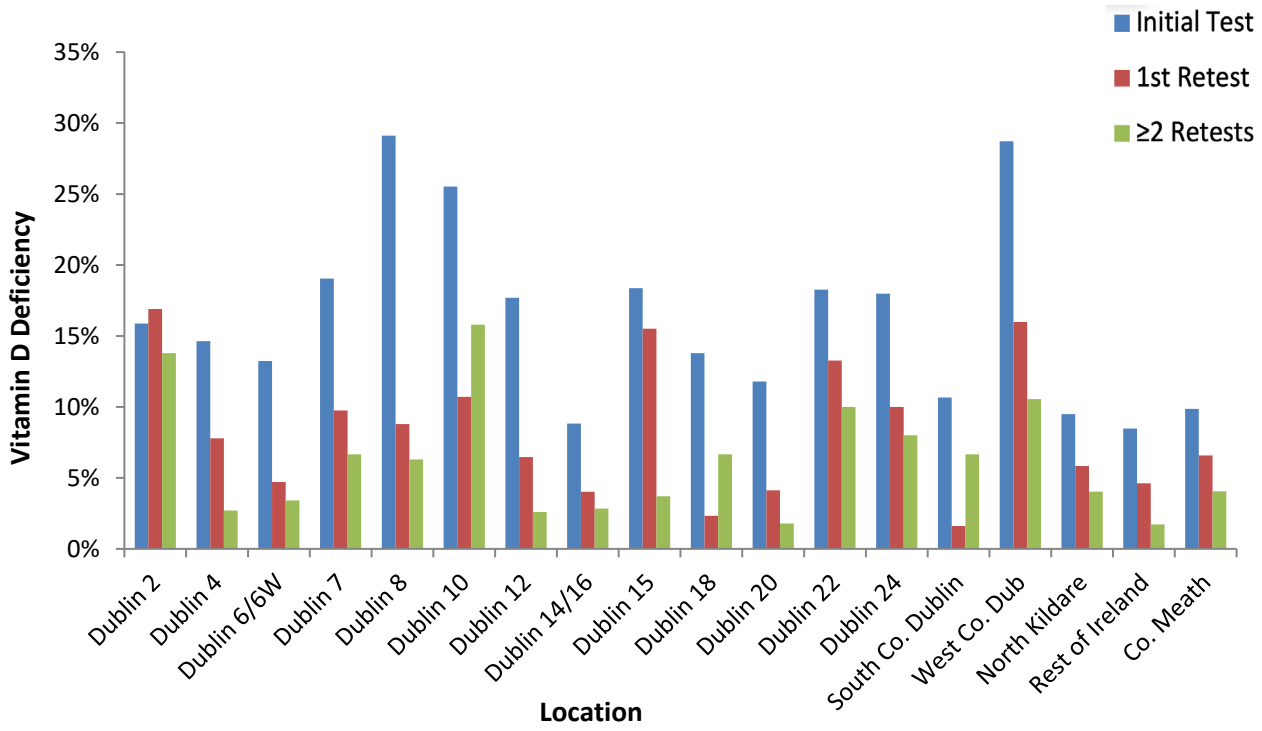


Figure 4.2 Summer Rates of Vitamin D Deficiency by Location

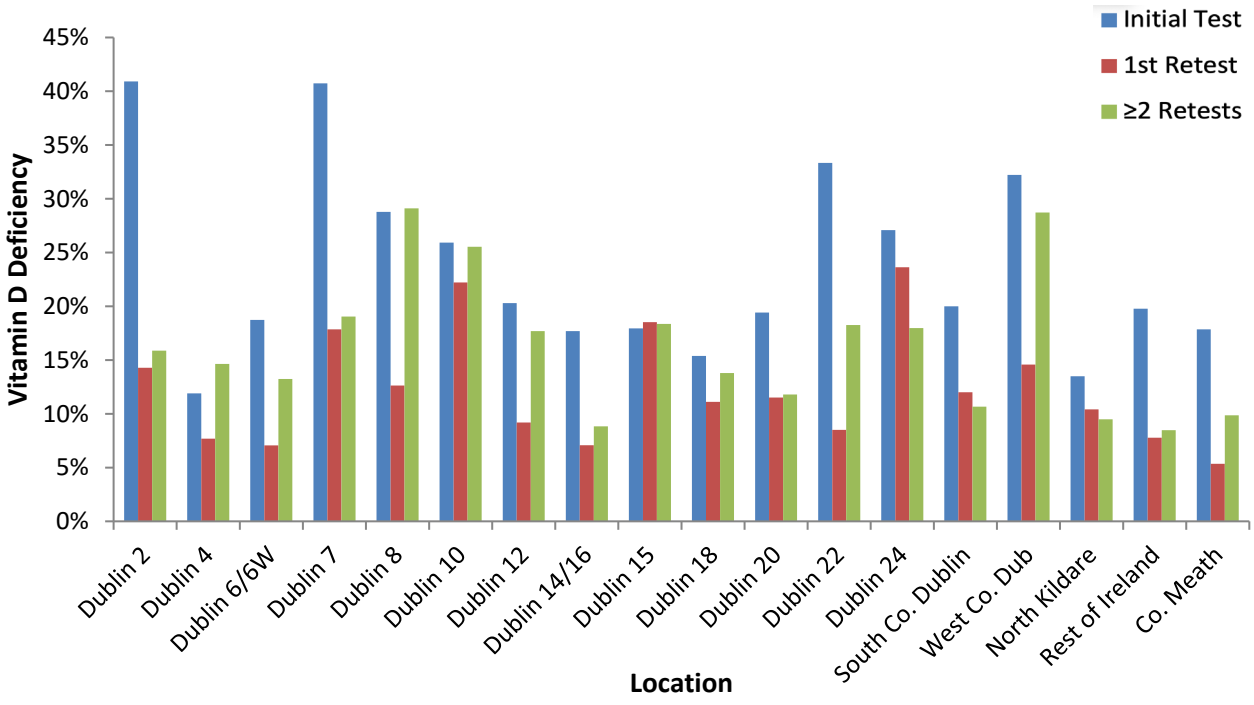


Figure 4.3 Winter Rates of Vitamin D Deficiency by Location

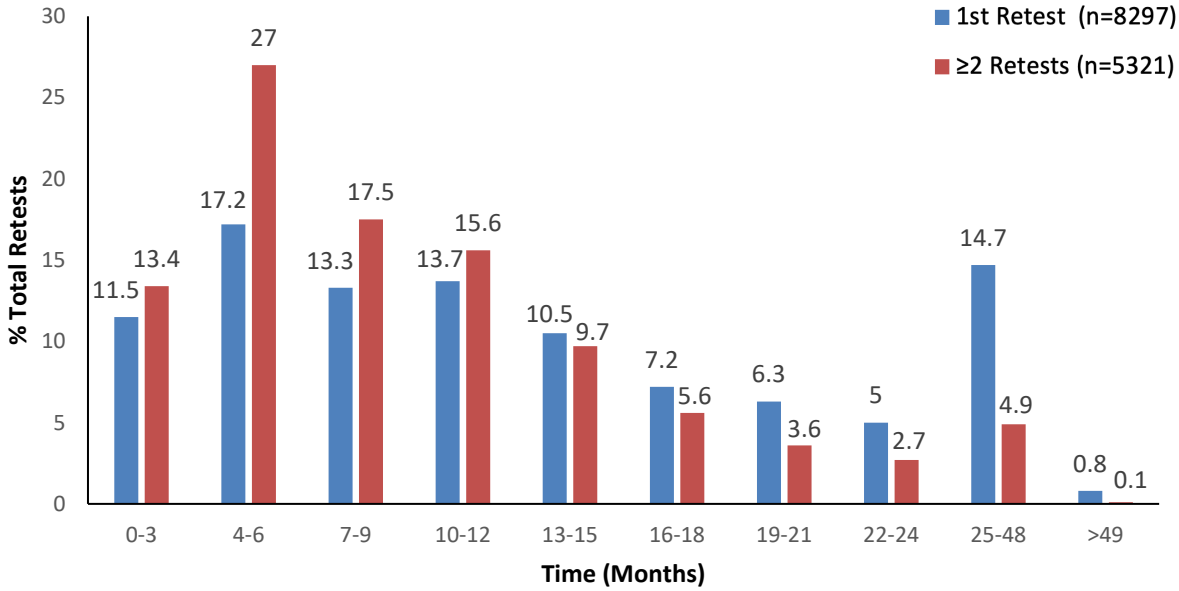
Table 4.4 Cohort Characteristics of Retested Patients

	Initial test	First Retest	*P*-value	≥2 Retests	*P*-value
	8,305	**8,305**		**5,325**	
25(OH)D[a]	51.5 (32.0)	62.5 (31.1)	**<0.001**	67.2 (30.3)	**<0.001**
<30 nmol/L (%)	18	9	**<0.001**	6	**<0.001**
30-49.9 nmol/L (%)	25	19	**<0.001**	17	**<0.001**
>125 nmol/L (%)	3	4	**<0.001**	5	0.151
Female	6013	6013		3813	
25(OH)D[a]	52.9 (32.7)	64.3 (31.6)	**<0.001**	68.7 (30.7)	**<0.001**
<30 nmol/L (%)	17	8	**<0.001**	5	**<0.001**
30-49.9 nmol/L (%)	24	17	**<0.001**	16	**0.013**
>125 nmol/L (%)	3	5	**<0.001**	5	0.305
Male	2292	2292		1512	
25(OH)D[a]	47.9 (29.6)	57.8 (29.1)	**<0.001**	63.6 (29.1)	**<0.001**
<30 nmol/L (%)	20	10	**<0.001**	6	**<0.001**
30-49.9 nmol/L (%)	28	23	**<0.001**	19	**0.001**
>125 nmol/L (%)	2	3	**0.004**	4	0.095
Age Categories (yrs)	8305	8305		5325	
18-39[a]	39.8 (31.6)	52.8 (30.6)	**<0.001**	55.0 (31.4)	0.273
40-49[a]	45.9 (29.9)	56.1 (32.6)	**<0.001**	59.6 (29.7)	0.133
50-59[a]	54.5 (31.5)	63.4 (30.2)	**<0.001**	66.2 (30.3)	0.244
60-69[a]	60.7 (30.5)	69.9 (28.8)	**<0.001**	73.9 (29.0)	**0.002**
70-79[a]	62.5 (30.9)	71.0 (29.7)	**<0.001**	73.6 (28.6)	0.331
80-89[a]	55.3 (31.8)	68.7 (30.9)	**<0.001**	74.1 (29.3)	0.109
>90[a]	62.5 (31.7)	66.3 (30.4)	0.893	79.2 (36.6)	0.172

[a]Indicates results reported as Geometric Mean (SD) quoted as nmol/L. The *P*-value for Bonferroni correction is 0.0013. Independent sample t-tests for continuous and cross tabulation with Chi-squared and ANOVA for categorical were used. *P*-value expressed with respect to initial test vs. first retest and first retest vs. ≥2 retests, significant at $P < 0.05$ (bold).

4.3.4 Time to Retest

12.2% of retests were completed within 3 months, as were 13.4% of ≥2 retests (Figure 4.4). The greatest number of first retests (17.2%) and subsequent tests (27.0%) were between 4 to 6 months. More than half of 1st retests (55.7%) and nearly three quarters (73.4%) of ≥2 retests took place within 12 months. However, a significant proportion of first retests (44.3%) and second retests (26.6%) occurred over one year later, though were not included as part of the definition of inappropriate testing. Predictors of retest within 3 months of an initial test were younger age (55.2yrs ± 17.4 vs. 55.9yrs ± 16.2, *P*<0.001) but there was no difference in baseline 25(OH)D (71.4 ± 33.0 nmol/L vs. 69.9 ± 30.8 nmol/L, *P*=0.452) or female sex (74.6% vs. 72.1%, *P*=0.058).



Time to ≥2 retests includes the time between the 2nd or later retests and the closest previous retest.

Figure 4.4 Time Difference Between Vitamin D Retests

4.3.5 Cost Analysis

The number needed to test (NNT) to identify one person with deficiency, insufficiency, and levels >125 nmol/L at different testing points is shown in Table 4.5. The NNT to detect deficiency increased with the number of tests, ranging from 6 on initial testing to 17 on retesting. The NNT to detect excess vitamin D (>125 nmol/L) varied from 20-33. The NNT for deficiency was highest in 60-79 years and lowest in 18-39 years. NNT to detect deficiency varied by area across testing points.

Assuming €40 per vitamin D test, the cost of identifying one case of deficiency on initial testing ranged from €120 in those aged 18-39 years to €400 in those aged 60-79. On subsequent testing this rose to €1000 or more. Retesting costs within 3 months of an initial test was €66,560. Furthermore,

29% of retests comprised a second or later retest within 12 months costing of €156,240. Additionally, 26% of first retests were in those with an initial 25(OH)D level between 50-74 nmol/L costing €87,080. The total expenditure of inappropriate testing was €309,880 or €61,976 per year.

Table 4.5 Cost Analysis of 25(OH)D Testing

	Initial test	1st Retest	≥2 Retests	Initial test	1st Retest	≥2 Retests
	NNT	NNT	NNT	€	€	€
25(OH)D (nmol/L)						
<30	6	11	17	240	440	680
30 - 50	4	5	6	160	200	240
>125	33	25	20	1330	1000	800
Sex (<30 nmol/L)						
Female	6	13	20	240	500	800
Male	5	10	17	200	400	600
Age (Yrs)(<30 nmol/L)						
18-39	3	6	7	120	240	280
40-49	5	8	11	200	320	800
50-59	7	13	20	280	520	800
60-69	10	25	33	400	1000	1320
70-79	10	25	33	400	1000	1320
80-89	6	17	25	240	680	1000
<90	7	7	33	280	280	1320
Location (<30 nmol/L)						
North Co. Dublin	4	8	13	160	320	520
South Co. Dublin	6	14	20	240	640	800
West Co. Dublin	4	7	10	160	280	400
Co. Kildare	9	13	25	360	520	1000
Rest of Ireland	6	25	17	240	1000	680

Number Needed to Test (NNT) was calculated by dividing the percentage with deficiency, insufficiency or 25(OH)D >125 nmol/L into 100 in each category (age, sex, location, and retest point). The cost was calculated by multiplying the NNT by €40.

4.4 Discussion

Vitamin D retesting is common with one in four adults getting retested by their GP. Over 12% occurred within 3 months and a third represented ≥2 retests within the previous year. Those with vitamin D deficiency or insufficiency, female and aged 60-69 were more likely to get retested. Moreover, living in certain locations predicted greater likelihood of retesting. Over half (57%) of first retests were in vitamin D replete individuals, the majority of which may be considered inappropriate. As found elsewhere, vitamin D retests constituted a significant proportion of all requests [355, 365]. This may be due to increased patient led demand following greater public awareness of vitamin D with increased media reports of possible but yet unproven health benefits [14, 355, 365]. Despite the high number of vitamin D tests, there was no rise in retests over the five-year study period.

4.4.1 Factors Associated with Retesting

Females constituted the majority of tests as reflected in other studies [27, 365, 366], despite having a lower rate of deficiency and insufficiency. More females experience osteoporosis, an indication for testing, but have higher rates of GP attendance and health seeking behaviour compared to males [67, 341]. As discovered elsewhere, those with initial vitamin D deficiency or insufficiency are more likely to have recurrent testing, explained by the need to assess supplementation efficacy and compliance [359, 367]. Age was a predictor of retesting, with those aged 18-39 least likely to be retested and most likely to be deficient, as previously found [355]. In retested patients, we found an improvement in vitamin D status in nearly all age categories between initial and first retest, with a mean increase in 25(OH)D of 11 nmol/L. This increase is modest given a rise of up to 5.0 nmol/L per 100 IU of vitamin D supplemented may be expected [237], dependant on baseline 25(OH)D and dose provided, with consideration of the measurement technique and season also required [368, 369]. Importantly, the overall prevalence of deficiency in this study was halved on first retest (9%), dropping to 6% on further retests.

Over half (57%) who were retested were vitamin replete. The reasons for this are unclear though some guidelines suggest aiming for a vitamin D level of 75 nmol/L [30]. While vitamin D deficiency fell considerably between initial and repeat tests, nearly one in four (23%) remained deplete after two or more retests. Factors such as poor compliance with supplements and inappropriately early retesting may account for this [370]. Additionally, GPs may reassess vitamin D status based on seasonality or monitor for excess vitamin D [365]. Serum 25(OH)D typically drops by 10-20 nmol/L between late summer and winter and so this must be factored in when interpreting results and the

need to retest. Indeed, 3% had levels above 125 nmol/L in our study and testing has also been found to be nearly four times higher in those on supplements [366].

Location was a predictor of retesting independent of age and initial vitamin D status, suggesting different reasons for GP requests by area. Patient led requests may account for some retesting and may be more likely in higher socioeconomic areas which is associated with greater health seeking behaviours such as GP attendance [371]. In Switzerland, those with a higher level of health insurance and living in urban areas were more likely to get tested [366]. In Ireland, 43% of the population have medical cards providing access to free GP care, which might influence patient led demand for vitamin D testing [372]. Patient reassurance has been identified as strong motivation for GPs to perform diagnostic tests [364]. In particular, maintaining a good relationship, avoiding conflict, and creating good will for future consultations has been cited with regard to vitamin D testing [364]. A 'test me and treat me' patient perspective has also been noted in one study towards vitamin D testing and supplementation, with a focus on vitamin D in strongly medicalised terms [373]. It has been suggested that increased lay interest from science publications in the media, medicalisation of vitamin D and clinical uncertainty around testing may have fuelled recent the rise in tests [14, 373].

4.4.2 Inappropriate Retesting and Cost

We found 12% of retests were completed within 3 months and two or more retests were done within one year in nearly a third of cases. Similar retesting rates within short periods have been previously reported, with 20% of retests occurring within 3 months [365], and 38% taking place within 6 months [355]. In Canada, 40% of vitamin tests were inappropriate, defined as a retest within 3 months or more than two tests within one year [374]. Retests within 3 months may be considered redundant as it does not allow sufficient time for therapeutic correction of vitamin D deficiency [365, 375]. The significant level of early and repeat retesting is likely due to a lack of awareness of guidelines though these are limited with most focusing on indications for initial testing. In addition, our laboratory like most in Ireland does not have a system in place at the point of ordering serum 25(OH)D that could help to eliminate inappropriate requests.

Annual expenditure on inappropriate vitamin D testing was €61,976 comprising those retested within 3 months, those retested who had initially levels between 50-74 nmol/L or two or more retests in the same year. There were large variances in the NNT to detect deficiency across population demographics and locations. Testing the youngest adults (18-39yrs) was the most cost effective with €120 spent for every case of deficiency identified, increasing to €400 in those aged 60-

79 and over €1000 on retesting. Even at a cost of £12-20 per vitamin D test in the UK, the sheer volume of tests can result in substantial expenditure, placing pressure on the health service [14, 355].

4.4.3 Strategies to Reduce Inappropriate Vitamin D Testing

Excess vitamin D testing and rising costs have been highlighted in many countries, with different strategies employed to curb this. The solutions fall into two categories: (1) computer-based interventions at the point of ordering to reduce the number of inappropriate and unnecessary tests and (2) population-based approaches, via supplementation or fortification, to eliminate deficiency and reduce the need for 25(OH)D monitoring.

Computer mediated interventions include two approaches. The first is a 'soft' stop where a pop-up reminder of criteria for vitamin D testing indications are presented, with an alert if there is no corresponding match of patient records to clinical guidelines [376, 377]. The second is a 'hard approach', where the test is limited to specific conditions [358, 359, 378, 379], certain medical specialties [377] or requesting algorithms, limiting repeat tests within specific time periods [380]. These strategies using different criteria have been utilised with varying levels of success and have resulted in reductions in vitamin D testing in the US [376], Denmark [359], Canada [378] and Italy [380]. In particular, in Alberta, Canada, there was a 92% reduction in testing while still including all relevant clinical indications [378]. However, in Australia the introduction of new testing criteria in 2014 resulted in an initial drop in requests, it was followed by an 8-13% increase in all age groups between 2016 and 2019 [381]. Different clinical indications between countries may partially explain the variation. For example, the guidelines are broader in some countries such as the US and Denmark [359, 376] and more restrictive in others including France and Canada [357, 378].

Another solution suggested by the Endocrine Society is population supplementation to decrease vitamin D deficiency and reduce the need for testing [30]. This may be considered an option as it remains unclear whether increased testing results in improved vitamin D status at a population level [14]. Alternatively, food fortification is another strategy. In Finland, after fortification of fat spreads and milk products, 91% of the population are now vitamin D sufficient (>50 nmol/L) though studies on its effect on testing are lacking [218]. In a modelling study of vitamin D deficiency in England and Wales, the estimated saving from fortification of wheat flour far outweighed the healthcare costs of preventing vitamin D deficiency, even without considering the economic burden of vitamin D testing [382]. However, genetic disorders such as 24-hydroxylase deficiency which increase the risk of vitamin D toxicity and hypercalcaemia need to be factored in when

considering widespread fortification. Of note, supplementation of at-risk adults without prior vitamin D testing has been advocated during the current pandemic, given the potential benefits of vitamin D on either preventing COVID or reducing its severity [383].

In summary, given increasing vitamin D requests and high proportion of retests, strategies to promote appropriate testing would be helpful to curb mounting costs. Retesting should be considered where compliance with supplements is in question, malabsorption is suspected or in conditions such as osteomalacia/osteoporosis and hyperparathyroidism [361]. Retesting should generally not occur within 3 months. Based on our study, it is evident clear guidelines for GPs on vitamin D retesting is needed. As previous research suggests this action alone will not suffice in reducing inappropriate requests [359] and should be coupled with interventions at the point of ordering vitamin D. However, in order to improve patients' status and reduce laboratory costs this needs to be combined with appropriate treatment. In Ireland, the HSE has recommended that a user-friendly general practitioner (GP) ordering system for vitamin D is developed in GP information systems [26]. However, this has yet to be implemented. In the future, other assessments of 25(OH)D that better gauge status over a longer time period might provide a better alternative to retesting such as hair measurements [384].

4.4.4 Strengths

This is the largest study to investigate vitamin D retesting in Ireland. Vitamin D was measured using the gold standard method of LC/MS with strict adherence to quality control measures. We included a large dataset collected over a 5-year period with data on geographical areas of testing, with vitamin D status across several time points. We also did cost evaluations for detecting deficiency within population demographics.

4.4.5 Limitations

We did not have information on the indications for vitamin D testing or retesting nor any data on patient medical history, medications or supplement use, biophysical factors, or sun exposure. We could not identify those who may have been tested before or after the study period meaning a proportion of patients may have been incorrectly categorised as non-retested.

4.5 Conclusion

Vitamin D testing is frequent with one in four adults getting retested by their GPs. Furthermore, 12.2% of all retests were done inappropriately early (within 3 months), a third too frequently and over half in initially vitamin D replete patients (>50 nmol/L). Differences in retesting by age, sex and location emphasize the need for clear national guidance for GPs on vitamin D testing Laboratory ordering systems that limit requests based on pre-defined criteria should be considered. Population based strategies to reduce vitamin D deficiency may be more effective than the current practice of testing.

Chapter 5: Low Socioeconomic Status Predicts Vitamin D Status in a Cross-Section of Irish Children.

This chapter has been published (July 2022) in *The Journal of Nutritional Sciences*, Publisher: Cambridge University Press, Impact Factor: 3.03

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The PDF of this manuscript can be found in Appendix Section C (ii): Thesis-related Publications

5.1 Introduction

Vitamin D deficiency (25(OH)D <30 nmol/L) in children can lead to impaired bone mineralisation, causing rickets or osteomalacia [8]. Concernedly, a case study of Irish infants in 2006 suggests a rise in rickets incidence [2], as found in the UK, where cases have reached a 50-year peak [385]. While the overall prevalence of rickets is low, those at increased risk include young children under 5 particularly those of Black and South-east Asian ethnicity [386].

Importantly, peak bone mass in adolescence and early adulthood is influenced by vitamin D status and may account for 60% of osteoporosis risk in later life [387]. Vitamin D may also have a role developmentally in early life consistent with the Barker foetal origins hypothesis [388]. For example, it may be important in foetal epigenetic programming of respiratory conditions in childhood [389] and has been associated with language and motor skill development, and risk of autism and ADHD [390, 391]. Deficiency in childhood has been associated in some studies with extra-skeletal diseases [391] such as hypertension [259], diabetes [58, 260], depression [261], dental caries [262], atopy and asthma [263, 264]. Additionally, vitamin D might support childhood immune function with evidence suggesting a protective effect against respiratory tract infections. However randomised control trials are required to further explore these associations [258].

While adult deficiency is known to be prevalent in Ireland [48, 154, 392], studies in children and adolescents are limited, with deficiency (<30 nmol/L) ranging between 5-22% and levels <50 nmol/L reported to be between 27-89% [54, 80, 108, 141]. Factors related to familial socioeconomic status (SES) have been suggested to affect vitamin D including lower diet quality, reduced intake of oily fish and supplement intakes and less access to outdoor amenities [47, 104, 105]. While some studies in Ireland have looked at the predictors of vitamin D, none have investigated any relationship with SES in children. In the UK, social deprivation and lower household income has been found to be independently associated with childhood vitamin D deficiency [90, 295].

Given the limited studies in Ireland, we aimed to assess the association of SES and vitamin D status in children (1-17 years) in the Dublin area and surrounds who had 25(OH)D levels tested at our hospital laboratory by request of their General Practitioner (GP). In addition, we aimed to identify the prevalence of deficiency and its variation by age, sex, and season. We also examined the proportion of children who were retested, and factors associated with this.

5.2 Method Particular to this Chapter

Full details of methods including Ethical Approval and Serum 25(OH)D is specified in Chapter 2, methods section 2.1 and 2.2 respectively. Methods unique to this chapter are outlined below.

5.2.1 Data Collection

A convenience sample was identified from data collected between 2014-2020 using the following exclusion criteria: age ≥18 years on initial test, incomplete or missing demographic data, non-community address (e.g., Hospital) or location outside the Republic of Ireland. We also identified any repeat vitamin D tests (i.e., retests) for each participant during the study period. Full details regarding data collection are provided in Chapter 2, Section 2.3

5.2.2 Statistical Analysis

A general overview of the Statistical analysis procedure is given in Section 2.3. The population was dichotomised by age (≤12 or >12 years) as in previous studies [85, 95, 96] Independent factors associated with vitamin D deficiency were explored in multi-nominal logistic regression models using the following variables: age category, sex, socioeconomic status, and season of sampling. In a similar model, we explored for predictors of vitamin D retesting. Winter was defined as (October - February); and summer (March - September) as used elsewhere [25].

5.2.3 Socioeconomic Status

Participant socioeconomic status (SES) was assessed by mapping postal addresses using the 2016 Pobal HP (Haase-Pratschke) Deprivation Index [393]. This is a composite score of demographic profile, social class composition and labour market situation of small areas based on the 2016 Census of the Population. Small areas (100 households mean) are given a Relative Index Score that is then categorised into the following groups; extremely disadvantaged (≤-30), very disadvantaged (-20 to -29.99), disadvantaged (-10 to -19.99), marginally below average (0 to -9.99), marginally above average (0 to 9.99), affluent (10 to 19.99), very affluent (20 to 29.99) and extremely affluent (≥30). In this analysis, categories were combined into four groups (1) disadvantaged (extremely disadvantaged, very disadvantaged, disadvantaged) (2) below average (3) above average, and (4) affluent (extremely affluent, very affluent, affluent), as previously described [394].

5.3 Results

Demographics of the cohort are shown in Table 5.1. Vitamin D results (not including retests) were initially identified for 1,294 children aged between 1-17 years. After exclusion of participants with no available address (n=25), and in whom SES could not be mapped (n=43) the final number was 1226. The majority (69.2%) were female and 89.3% were aged >12 years. A similar proportion were tested in summer (56.5%) and winter (43.5%). The most prevalent SES classification was above average (43.6%), followed by affluent (37.5%), below average (11.1%) and disadvantaged (7.8%). The number tested was lower in 2014/2015 with annual increases thereafter in the period up to 2019. Nearly one fifth (17.6%, n=228) of participants had vitamin D retested in the study period.

Table 5.1 Population Demographics

Category		**n**	**%**
Age	≤12 years	131	10.7
	>12 years	1095	89.3
SES	Affluent	460	37.5
	Above Average	534	43.6
	Below Average	136	11.1
	Disadvantaged	96	7.8
Season	Winter	533	43.5
	Summer	693	56.5
Sex	Female	848	69.2
	Male	378	30.8
Year	2014	74	6.0
	2015	103	8.4
	2016	191	15.6
	2017	188	15.3
	2018	214	17.5
	2019	241	19.7
	2020	215	17.5
Total		1226	

SES; Socioeconomic Status, Winter; October to February, Summer; Mar-Sept

Overall, 23% were vitamin D deficient, ranging from 20.1% in summer to 25.9% in winter (Table 5.2). More than half (50.6%) had levels below 50 nmol/L, which was more common in winter compared to summer (55.3% vs. 46.9%, *P*=0.003). Mean 25(OH)D was higher in those aged under vs. older 12 years (43.3 nmol/L vs. 49.5 nmol/L, *P*=0.020). It was also lower in females vs. males (42.3 nmol/L vs. 47.6 nmol/L, *P*=0.008) but the difference was only significant in winter (39.4 nmol/L vs. 45.7 nmol/L, *P*=0.021). Serum 25(OH)D also varied by year ranging from an average of 39.1 nmol/L in 2018 to 50.7 nmol/L in 2014 (P <0.001).

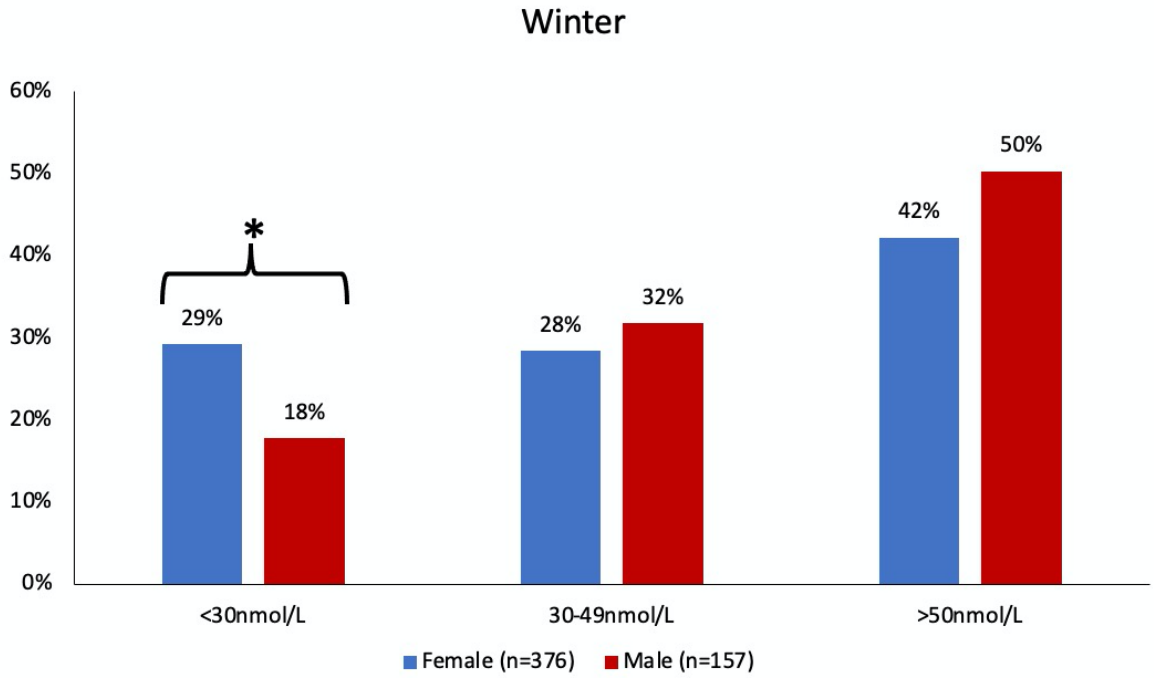
Females had a higher prevalence of deficiency vs. males (25% vs. 17%, *P*=0.003) but this remained significant only in winter (29% vs. 18%, *P*=0.006) (Figure 5.1). There was also a lower proportion of females vs. males who were vitamin D sufficient (≥50 nmol/L) in both seasons but this was not statistically significant. The overall prevalence of 25(OH)D >125 nmol/L was 0.6% (range 126-174 nmol/L) with no difference by season or sex. The highest corrected calcium level among these participants was 2.6 nmol/L.

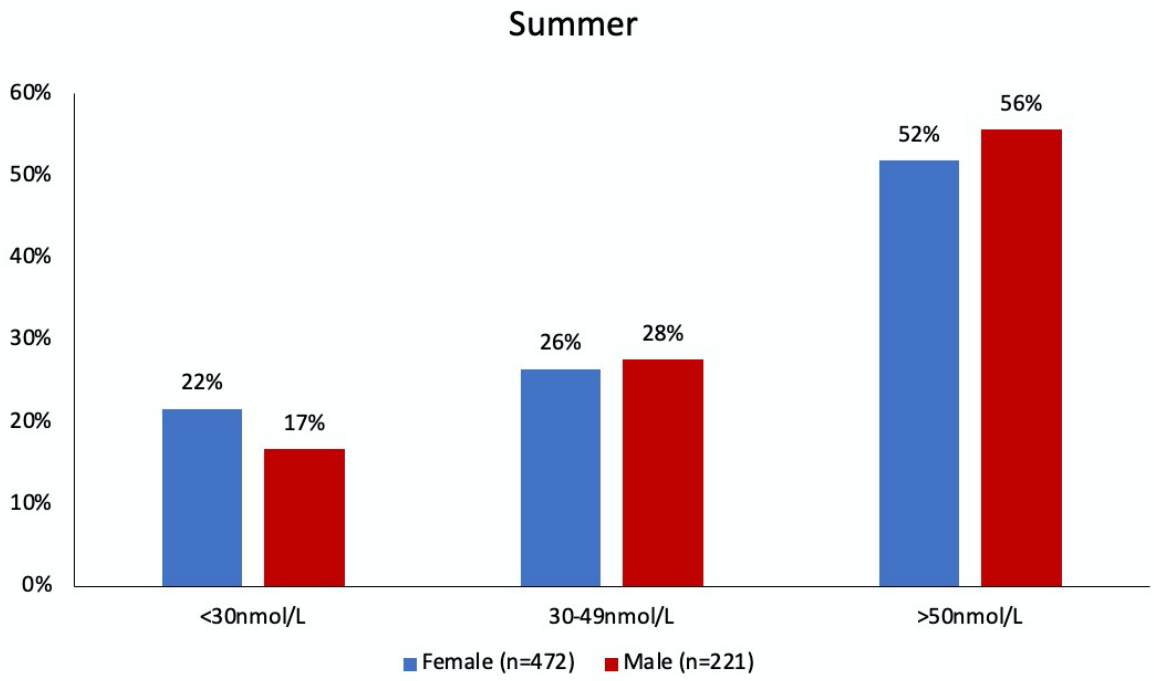
Vitamin D deficiency was more prevalent in those aged over vs. under 12 years (23% vs. 15%, *P*=0.034). In the over 12s, deficiency was also greater in winter vs. summer (27% vs. 21%, *P*=0.021) (Figure 5.2). Those aged over 12 years had more sufficiency in summer vs. winter (53% vs. 43%, *P*=0.002). We also found more deficiency in those ≤12 years in summer vs. winter but this was not statistically significant. The prevalence of serum 25(OH)D >125 nmol/L was a respective 0.7% and 0.5% in the under and over 12's. Overall, levels of deficiency were significantly higher (26% vs. 20%, *P*=0.015), and sufficiency significantly lower (45% vs. 53%, *P*=0.003), in winter versus summer.

Table 5.2 Serum 25(OH)D Status and Concentration by Age and Sex (Dichotomised by Season)

Category	n	Total	*P*-value	n	Winter	*P*-value	n	Summer	*P*-value
25(OH)D	1226	43.9 (25.3)		533	41.2 (24.4)		693	46.1 (25.7)	**<0.001**
<30 nmol/L (%)	277	22.6		138	25.9		139	20.1	**0.015**
<50 nmol/L (%)	620	50.6		295	55.3		325	46.9	**0.003**
Sex									
Female	848	42.3 (25.3)	**0.008**	376	39.4 (24.8)	0.021	472	44.8 (25.5)	0.148
Male	378	47.6 (25.0)		157	45.7 (23.1)		221	49.0 (26.2)	
Age									
≤12 years	131	49.5 (25.4)	**0.020**	56	46.8 (21.3)	0.053	75	51.6 (27.9)	0.147
>12 years	1095	43.3 (25.2)		477	40.5 (24.7)		618	45.5 (25.4)	

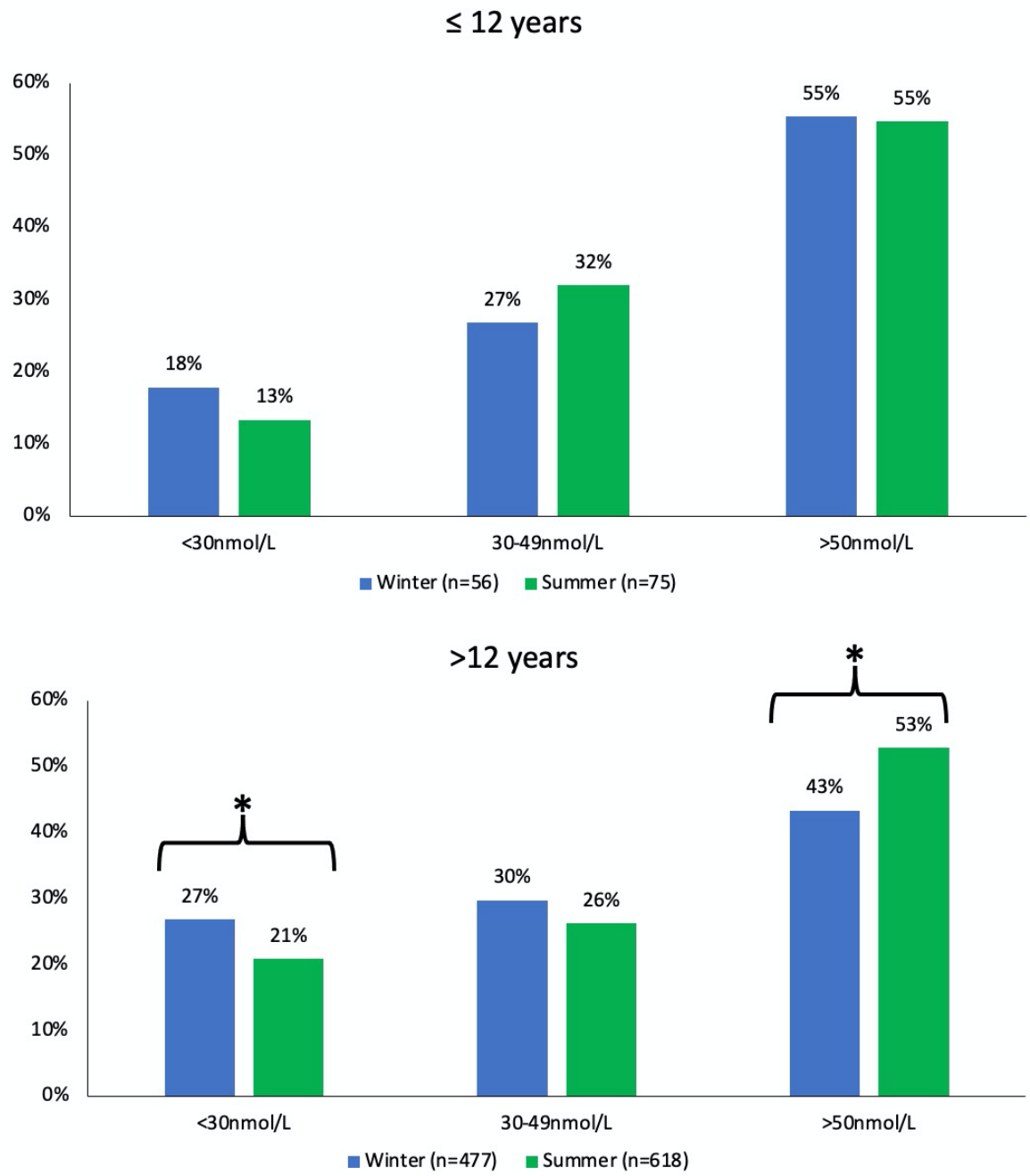
25(OH)D reported as Geometric mean ±(standard deviation) in nmol/L. *P*-value for winter season (Oct-Feb) vs. summer season (Mar-Sept). *P* -values are reported for within category differences, using Mann-Whitney U or Chi squared, significant at $P<0.05$ (bold).





*Indicates significance (P<0.05) analysed by Chi-square. Winter (Oct-Feb); Summer (Mar-Sept)

Figure 5.1 Vitamin D Status by Sex



*Indicates significance (P<0.05) analysed by Chi-square. Winter (Oct-Feb); Summer (Mar-Sept)

Figure 5.2 Vitamin D Status by Age

Vitamin D status and concentration by socioeconomic category is presented in Table 5.3. The difference in vitamin D status was greatest between affluent and disadvantaged areas. Children in below or above average areas had intermediate vitamin D levels with little difference between these SES categories, though being higher than disadvantaged. There were also significant differences in deficiency by area (P=0.0018) ranging from 34% in disadvantaged to 20% in affluent areas. Similarly, the lowest prevalence of levels below 50 nmol/L was identified in affluent compared to

disadvantaged areas (46% vs. 61%, *P*=0.019) (Figure 5.3). When comparing below and above average SES, there was no difference in the prevalence of deficiency (*P*=0.866) or levels between 30-49 nmol/L (*P*=0.312). There were no significant differences in serum 25(OH)D in females (*P*=0.051) or males (*P*=0.127) across SES categories, but samples sizes were smaller. In both those over and under 12 years, there were significant difference in vitamin D status (P <0.05) by SES with higher levels in affluent areas. Summertime vitamin D status was also significantly different across SES categories (*P*=0.010) and highest in affluent areas.

Table 5.3 Serum Concentration 25(OH)D by Socioeconomic Status Category

		Socioeconomic Status Category				
nmol/L	**n**	**Disadvantaged**	**Below Average**	**Above Average**	**Affluent**	***P*-value**
Overall	1226	38.1 (23.7)	43.0 (26.6)	43.1 (25.5)	46.5 (24.7)	**0.005**
<30 (%)	227	34	24	23	20	**0.018**
<50 (%)	343	61	49	53	46	**0.019**
Sex						
Male	378	37.7 (24.2)	47.5 (25.1)	47.3 (26.0)	50.4 (23.8)	0.127
Female	848	38.2 (23.7)	41.3 (27.2)	41.4 (25.1)	44.8 (25.1)	0.051
Age (years)						
≤ 12	131	36.9 (14.9)	57.6 (19.6)	44.3 (27.4)	56.2 (24.0)	**0.031**
>12	1095	38.1 (24.1)	41.2 (27.2)	42.9 (25.3)	45.5 (24.7)	**0.020**
Season						
Winter	533	37.3 (21.5)	39.5 (27.9)	40.6 (24.6)	43.0 (23.7)	0.271
Summer	693	38.6 (25.3)	45.7 (25.6)	44.9 (26.0)	49.8 (25.2)	**0.010**

25(OH)D reported as Geometric mean ±(standard deviation) in nmol/L. Winter (Oct-Feb); Summer (Mar-Sept). *P*-values are reported for within category differences, using Chi squared or Kruskal-Wallis test. *P*-value Indicates significance at <0.05 level (bold).

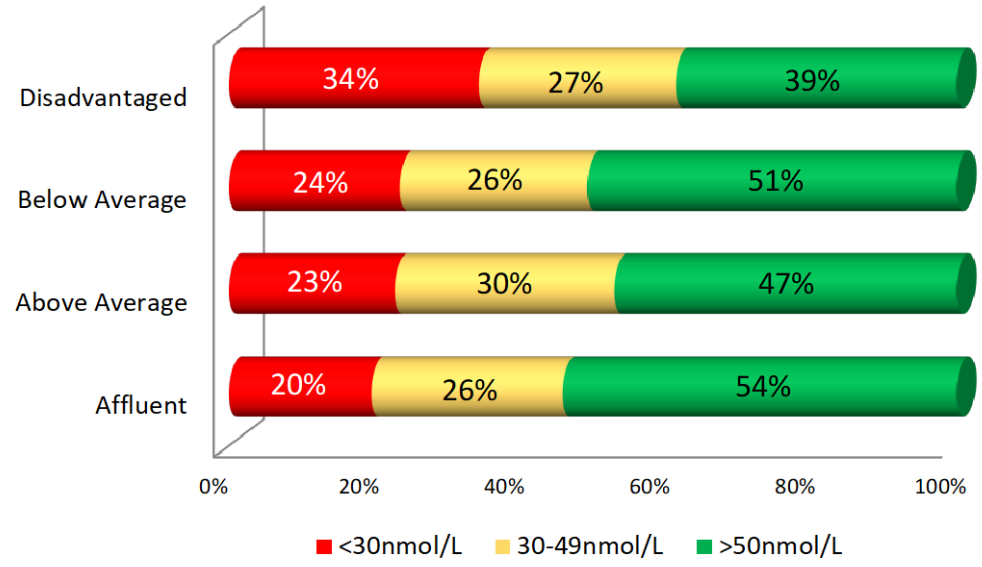


Figure 5.3 Vitamin D Status by Socioeconomic Status

Predictors of vitamin D deficiency are shown in Table 5.4. The greatest predictor was living in a disadvantaged location (OR 2.18, CI 1.34-3.53, *P*=0.002), followed by female sex (OR 1.57, CI 1.15-2.14, *P*=0.005), and testing in the winter (OR 1.40, CI 1.07-1.84, *P*=0.015). Age was not an independent predictor, though the number under 12 years was small (n=139) and the analysis likely to be underpowered to detect a significant difference.

Table 5.4 Predictors of Vitamin D Deficiency (in Multinomial Regression Model)

Deficient (<30 nmol/L) vs. Non-deficient (≥30 nmol/L)	n	B	OR	Confidence Interval		*P*-value
				Lower	Upper	
Intercept	1226	-1.863				
Age ≤12 years	131	-0.47	0.625	0.379	1.032	0.066
Age >12 years†	1095					
Disadvantaged	96	0.778	2.176	1.34	3.534	**0.002**
Below Average	136	0.256	1.292	0.814	2.052	0.277
Above Average	534	0.222	1.249	0.917	1.702	0.159
Affluent†	460					
Female	848	0.451	1.569	1.149	2.144	**0.005**
Male†	378					
Winter	533	0.338	1.402	1.069	1.840	**0.015**
Summer†	693					

B; Unstandardised Beta, OR; Odds Ratio. *P*-value Indicates significance at <0.05 level (bold). †Indicates reference variable. Winter (Oct-Feb); Summer (Mar-Sept).

Predictors of vitamin D retesting are shown in Table 5.5. Baseline deficiency was the greatest predictor (OR 1.77 CI 1.22-2.56, *P*=0.003), followed by insufficiency (OR 1.76, CI 1.24-2.49, *P*=0.002) and female sex (OR 1.45 CI 1.03-2.03, *P*=0.032). There was a trend for reduced testing in those living in disadvantaged (OR 0.55 CI 0.29-1.05, *P*=0.068) and above average locations (OR 0.72 CI 0.52-1.00, *P*=0.052).

Table 5.5 Predictors of Retesting (in Multinomial Regression Model)

Retested vs. Not Retested	n	B	OR	Confidence Interval		*P*-value
				Lower	Upper	
Intercept	1226	-1.905				
Age ≤12 years	131	-0.08	0.923	0.561	1.52	0.754
Age >12 years†	1095					
Disadvantaged	96	-0.59	0.554	0.294	1.045	0.068
Below Average	136	-0.158	0.854	0.521	1.401	0.532
Above Average	534	-0.324	0.723	0.521	1.003	0.052
Affluent†	460					
Female	848	0.372	1.45	1.032	2.038	**0.032**
Male	378					
Winter	533	0.011	1.011	0.75	1.364	0.941
Summer†	693					
Deficient <30 nmol/L	277	0.568	1.765	1.216	2.562	**0.003**
Insufficient 30-49 nmol/L	343	0.562	1.755	1.238	2.486	**0.002**
Sufficient >50† nmol/L	606					

B, Unstandardised Beta; OR, Odds Ratio. *P*-value Indicates significance at <0.05 level (bold). †Indicates reference variable. Winter (Oct-Feb); Summer (Mar-Sept).

5.4 Discussion

This is the largest investigation of vitamin D status in a convenience sample of Irish children and adolescents and the only one to explore the association with SES. We identified that 23% overall were vitamin D deficient (<30 nmol/L), rising to 34% in children living in disadvantaged areas. In total half of the cohort had concentrations less than 50 nmol/L, indicating that inadequate vitamin D status is highly prevalent. The greatest predictor for deficiency was living in disadvantaged locations, followed by female sex, and testing in the winter (October - February). Those over 12 also had lower vitamin D status than those under 12 years. We also showed that about one in five children were retested which is similar to that found in Irish adults [15], with predictors of retesting including initial deficiency/insufficiency and female sex.

5.4.1 Vitamin D Status by Socioeconomic Status

Children living in disadvantaged areas were more than twice as likely to be vitamin D deficient compared to affluent children. This is the first study in Ireland examining the effect of SES on vitamin D status in children. The only other Irish study investigating vitamin D status and SES was in older adults as part of the TILDA study, which found that those with below average asset wealth had 1.5 times increased prevalence of vitamin D deficiency [48]. In the UK low socioeconomic status has also been associated with greater deficiency [90, 295] and similar results have been identified in the Netherlands [249], Greece [395], and Canada [253].

Lower SES may impact on vitamin D status as it has been associated with factors (e.g., reduced physical activity outdoors) that may lower UVB exposure [396], reduced dietary and supplemental vitamin D intake and greater obesity prevalence [47, 104, 105]. Supplements are a key contributor of vitamin D intake in Irish children and adolescents [100, 220]. However, low supplement use has previously been found in children in low income or food insecure households [105] and has also been correlated with parental education [397]. Total vitamin D intake has been identified as being lower in children in lower income families in the UK and Spain [398, 399]. This may be due to an increased prevalence of unhealthy eating in low SES children with lower consumption of vitamin D rich foods including oily fish, meat, and fortified food [104, 400, 401]. Furthermore, lower serum 25(OH)D has been found in Canadian children (n=1753) from lower income families [402]. Studies of Irish adults have also found an association with disadvantaged backgrounds and a lower likelihood of meeting dietary vitamin D intake recommendations [107] with lower consumption of foods that are typical sources of vitamin D including fish, meat, and breakfast cereals. In the US, vitamin D intake in

children and adults was also correlated with income, with greater levels shown in the highest income group [403, 404].

Another factor that may help explain vitamin D status by SES group is differences in rates of obesity. For example, obesity or overweight status in Irish children was more prevalent in those attending disadvantaged schools [405]. Obesity is associated with lower vitamin D in children, possibly due to its sequestration in adipose tissue [406]. We also identified seasonal differences in vitamin D status across SES categories, with those in affluent areas having higher serum levels in summer. This could be related to increased sun holiday travel, which is a reported determinant of vitamin D status in Irish adults [46] Additionally, higher socioeconomic status is associated with reduced screen-time, increased access to outdoor activities and engagement in organised sports in adolescents, resulting in increased sun exposure [47, 407, 408]. In deprived areas, there may be reduced access to parks/playgrounds/gyms, which could also lower UVB exposure [408, 409].

5.4.2 Vitamin D Status by Age

We identified that children aged >12 years had a greater prevalence of deficiency consistent with other studies in Europe, US, and Asia [90, 163, 257, 410]. The only other Irish study comparing vitamin D status by age category was small (n=252) and found a lower mean 25(OH)D in 12-17 years old versus those aged 1-4 years [54]. A larger Irish study of toddlers (aged 2 years) found a prevalence of deficiency (4.6%) about five times lower than in the over 12s in our study [141]. Similarly, in the most recent UK National Diet and Nutrition Survey, deficiency was greater in those aged 11-18 (19%) versus 4-10 years (2%) [256]. In Europe, higher rates of deficiency (<30 nmol/L) were found in teenagers versus younger children [163]. Likewise, in a large US study (n=16,180), over 12s had the greatest prevalence of serum 25(OH)D (<50 nmol/L) [271]. Lower vitamin D status in older children may reflect reduced intake of vitamin D fortified foods, more sedentary behaviour or screen time and higher rates of obesity [85, 95, 257]. Indeed, a dietary survey (n=594) of Irish children and teens found a lower rate of supplement use and fortified foods in adolescents (13-17 years) versus younger children (9-12 years) [100]. Increased vitamin D requirements in adolescence [87] due to an intensive period of new bone growth has also been proposed as a factor [29]. Finally, greater diagnosis of deficiency in older children might be in part due to more frequent presentation to GPs for chronic pain/medical symptoms or higher thresholds for vitamin D tests in younger children due to the challenges of phlebotomy [295].

5.4.3 Vitamin D Status by Season and Sex

As expected, there was a seasonal variation in 25(OH)D, consistent with most studies [54, 90, 252, 254], with more deficiency in winter versus summer. Furthermore, 55.5% of children had a 25(OH)D below 50 nmol/L in winter. This figure is identical (55.3%) to the recent finding in children (n= 47, age 7-11) living in Northern Ireland between November and March [108]. While prevalence of deficiency/insufficiency varied by season in the under 12s, the difference was not significant, but is likely explained by small sample size and lack of statistical power. A notable finding was the lower vitamin D status in females who were more likely to be deficient, a finding similar to other studies in Europe and elsewhere. For example, deficiency has been reported to be more common in Northern Irish female adolescents [137], female children in Britain [8, 90], Greece [276] and in the US [257]. Despite this, another study in Germany identified more deficiency in males [411].

We did find though that the difference in 25(OH)D status by sex was only significant in winter, albeit with a trend for better vitamin D status in males in summer. Dietary intake may be a contributory factor as female children have been found to have a lower vitamin D intake and consume less vitamin D fortified foods [86, 200, 331]. Body composition during puberty may play a role, with females acquiring greater fat mass during maturation [412]. Additionally, it is possible that adolescent girls may engage more in veganism, as found in female adults [413], which could lower vitamin D intake due to avoidance of meat and milks, that are significant sources of dietary vitamin D [85]. Females within ethnic minorities may also have reduced exposure due to religious dress [47]. On the other hand, male adolescents are reported to engage in more outdoor activity which affords more opportunity for sun exposure [90, 137]. They are also less likely to use sunscreen or take measures to avoid sunburn [414] and may have more cutaneous exposure to summer UVB due to less clothing cover [90, 415]. Finally, it has been suggested that higher overall GP consultation rates for girls than boys might account in part for a greater diagnosis of deficiency [295, 341].

5.4.4 Guidelines on Vitamin D Intakes and Implications

The Food Safety Authority of Ireland (FSAI) advise a vitamin D intake of 5 μg/day for children aged 1-5 years [2], with older children (age 6-11 years) advised to consume 10 μg/day [2, 4]. Guidelines are similar in the UK, with an intake (RNI) of 10 μg/day for those aged >4 years and a 'Safe intake' of 10 μg/day between 1-4 years [8]. However, the European Food Safety Authority (EFSA) and NAM recommend a higher dietary allowance of 15 μg/day between 1-18 years [416], replicated by the FSAI who recently updated advise for those older than 12 to receive 15 μg/day. Despite this increase of

recommendation guidelines in Ireland, previously 70-84% of 1-4 year olds [96] and 94% of 5-18 year olds had inadequate vitamin D intakes at the 5 μg/day and 10 μg/day level, respectively [85, 95].

Indeed, it has been suggested that vitamin D intakes for children may need to be substantially higher. For example, an estimated total vitamin D intake (dietary and supplemental) of 33.8 μg/day may be required for 97.5% of children living at 40-63°N to be vitamin D sufficient (>50 nmol/L) in the winter [201]. However, guidelines alone may not improve vitamin D status. In Canada, after dietary guidelines for vitamin D intake increased from 5 μg to 15 μg daily for those aged 1-70 years, an actual increase in vitamin D insufficiency (<50 nmol/L) was identified in those aged 6-18 years [254]. Targeted systematic vitamin D fortification of food is another option, as occurred in Finland in 2003. However, while it led to 91% of over 30's in the population achieving 25(OH)D >50 nmol/L [218], it produced little improvement in vitamin D intake or serum levels in adolescent females [331] who had lower fortified food consumption [88]. The significant prevalence of vitamin D deficiency in our cohort of children suggests that vitamin D intakes are inadequate for a sizeable proportion of those aged 1-17 years, particularly in disadvantaged areas. Guidelines on vitamin D intakes that are specifically tailored to include all Irish children should be developed. However, as studies show these measures alone tend to be inadequate, other strategies including targeted vitamin D fortification of foods that are consumed by children needs to be considered.

5.4.5 Strengths

This is the largest study of vitamin D status in Irish children (1-17 years), and the first to investigate the association with socioeconomic status. We used a specific measure of SES, that is localised to a small area of 100 households, whereas most other studies used proxy measures such as parental education or household income. We used the gold standard of vitamin D measurement, liquid chromatography tandem mass spectrometry (LCMS) and adhere to strict quality monitoring (participation in DEQAS). We also utilised a dataset collected over a 7-year period that included information on geographical areas and also explored for predictors of retesting.

5.4.6 Limitations

This study is based on a convenience sample of GP vitamin D requests which limits the generalisability of the findings to a wider population. In particular, there may be selection bias of study participants who may have conditions predisposing to vitamin D deficiency that underlies the reason for their testing. We were not able to account for factors that influence serum 25(OH)D including biophysical (ethnicity, body mass index, medical conditions) or lifestyle

(dietary/supplement intake, sun exposure or sunscreen use) due to the nature of the collected data. Finally, as the study is cross-sectional, we cannot infer any causality with regard to the factors we examined.

5.5 Conclusions

In conclusion, we identified that in a large convenience sample of children attending their GP in Ireland, those in the most disadvantaged area had the highest level of deficiency, affecting 34%. Furthermore, about one quarter of all children were found to be deficient. Childhood and adolescence are crucial periods for bone and muscle development, and deficiency may have long term effects on both skeletal and other health outcomes. Targeted and tailored guidelines on vitamin D intake for all Irish children as well as public health promotion of its importance should be a priority. Development of a systematic policy of a vitamin D fortification of foods regularly consumed by children could be a realistic approach to help mitigate this issue.

Chapter 6: Vitamin D: Determinants of Status, Indications for Testing and Knowledge in a Cross-Section of Irish Adults

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The PDF of this manuscript can be found in Appendix Section C (ii): Thesis-related Publications

6.1 Introduction

To date, most research on the determinants of vitamin D status in the Irish population have focused on older adults [43, 46, 48, 161]. Overall, studies point to supplement use as the most important determinant [43, 46, 48]. Several have identified a characteristic seasonal variation and found positive associations with proxy measures of sun exposure (sun enjoyment, sun holiday travel, geographical UVB irradiation and sunshine hours) [46, 78, 156]. However, none have looked at more specific markers of body exposure. Lower physical activity and frailty which may be indirectly linked to sun exposure, have also been associated with lower vitamin D status [46, 48]. Only four studies have investigated vitamin D status in a non-European ethnic demographic, finding lower 25(OH)D and a high prevalence of deficiency of between 57% and 88% [51-54]. Few have examined the association with dietary or specific food intakes though fortified milk, fish and egg consumption was found to be positive determinants in older adults and adolescents [46, 78, 137]. Biophysical factors such as increased BMI and female sex were also associated with lower vitamin D status in children and older Irish adults [43, 48, 62, 136, 137] while smoking, living alone and lower socioeconomic status have been found to be negative predictors [46, 48, 55].

Despite an increase in referrals for vitamin D testing in Ireland and evidence of up to a third being done inappropriately, no studies have explored the indications for these 25(OH)D assessments [15, 16, 154]. Furthermore, just one study investigated knowledge regarding vitamin D, but only in pregnant women where 70% had little awareness of dietary sources [52]. Given the lack of studies, we aimed to explore in detail the biophysical, lifestyle and dietary determinants of vitamin D status in a diverse population of adults. Furthermore, we aimed to explore for the first time in Ireland, indications for vitamin D testing, as well as adult knowledge of vitamin D.

6.2 Methods Particular to this Chapter

Detailed methods regarding Ethical Approval, Serum 25(OH)D Measurement and Statistical Analysis are outlined in Chapter 2, Sections 2.1, 2.2 and 2.4, respectively. Methods exclusive to this chapter are presented below.

6.2.1 Data collection

A convenience sample was identified from 25(OH)D results in 2020 using the exclusion criteria: age <18 years, incomplete or missing demographic data, non-community address (e.g., Hospital, Nursing home, Convent) or location outside the Republic of Ireland. A full description of the procedure for data collection is found in Chapter 2, Section 2.3.

6.2.2 Statistical Analysis

Median and interquartile range was used to report dietary intakes. Independent factors associated with vitamin D deficiency (<30 nmol/L) were explored in binary logistic regression models using the following variables and reference categories: age (≥50 years), sex (male), BMI category (normal weight), season of sampling (summer), ethnicity (Caucasian), smoking (non-smoker), alcohol (alcohol consumer), sun habits (sun-seeker), education (third level), and adherence to vitamin D RDA (no). Body exposure and hours spent in peak sunshine were co-correlated with sun seeking behaviour and were therefore not included in the model.

6.2.3 Participant Screening and Stratified Sampling

Of the 13,669 results collected, 1,639 were excluded due to incomplete data (n=423), age <18 (n=262), non-community address (n=239) and repeat samples (n=715) (Figure 6.1). This left a sample size of 12,060 from which we randomly selected a smaller number (n=100) of adults each into 12 groups defined by vitamin D status (<30, 30-49, 50-124 nmol/L), season (Winter /Summer) and age (above or below 50 years). We also selected an additional 4 smaller groups (n=15) with serum 25(OH) ≥125 nmol/L stratified similarly by age and sex. In this way, we were left with a sample of 1,260 adults with an equal distribution of age, vitamin D status and season of testing to which questionnaires were sent. Participants were contacted via postal address with an information sheet, consent form, and questionnaire which could be completed online (via link to survey monkey) or sent back manually in hard copy form in a pre-stamped, self-addressed envelope.

6.2.4 Questionnaire

The questionnaire we designed included 33 questions detailing medical information (indications for testing and pre-existing conditions that might affect vitamin D), biophysical (ethnicity, body mass index (BMI), body size [417], socioeconomic status (education level; third level or below), vitamin D intake (supplement and dietary intake) as well as dietary calcium intake using a food frequency questionnaire, lifestyle (smoking, alcohol intake) and sun exposure (time spent in peak sunshine, sunscreen use, body exposure, sun-seeking habits). Information also included data on participants vitamin D knowledge (awareness of health benefits and Recommended Dietary Allowance-RDA). Questionnaires were sent to individuals between March and June 2022 and answers to our survey related to the period in which they had serum 25(OH)D tested. Reasons for vitamin D testing were queried, with routine health checks, patient requests and fatigue considered inappropriate.

Ethnicity was dichotomised into Caucasian and non-Caucasian (Black, Asian-Chinese, Asian-other and mixed). Body Mass Index category was determined based on self-identification using a 10-image scale of body sizes representing underweight, normal weight, overweight and obese as validated by Harris et al., 2009 [417]. We asked if participants had any of the following conditions that could affect vitamin D status (gastrointestinal conditions e.g., Crohns, Coeliac Disease, Bowel/Stomach surgery, Inflammatory Bowel Disease), Cystic Fibrosis, Liver/Renal conditions, Pancreatic Disease and Eating Disorders.

Sun-seeking was categorised as no (avoid the sun) or yes (spend some time/seek the sun). Time spent outdoors was calculated based on the daily period spent outside between the hours of 1pm and 5pm during March to September [418]. Body Exposure was categorised as high, if more than face and hands were exposed on a sunny day and otherwise as being low.

6.2.5 Vitamin D/Calcium Intake

Dietary vitamin D (μg) from food sources (unfortified and fortified) and calcium intake (mg) was calculated using a food frequency questionnaire (FFQ) adapted from the TILDA questionnaire [48]. For each food consumed, an average vitamin D/calcium content per portion was estimated using food manufacturers information and Nutritics software Version 5.78 (Table 6.1). Where an approximate size of a food portion was not specified in the FFQ, an average portion size was assumed (e.g., =125 g pot). In order to estimate daily dietary calcium and vitamin D intake we initially calculated total weekly intake as follows: once per week (1 x unit food), 2-4 times per week

(3 x unit food), 5-6 times per week (5.5 x unit food), once per day (7 x unit food), 2-3 times per day (2.5 x unit x 7), 4-5 times per day (4.5 x unit x 7). The weekly total was then divided by 7 to give the total daily intake for vitamin D and calcium. We also dichotomised daily vitamin D intake from unfortified or fortified sources. The daily vitamin D intake from supplements (cod-liver oil, vitamin D only supplement, multivitamin containing vitamin D) was also calculated. Total daily vitamin D intake was then estimated by combining supplemental and dietary intake and those who met the Recommended Daily Allowance (RDA) were identified (10 μg/day as per advised by FSAI at the time of vitamin D sampling). We also identified those who exceeded the Tolerable Upper Intake level (UL) for vitamin D of 100 μg (4000 IU) per day [419] and who met the dietary calcium RDA (1000 mg/day in those aged 18-24 and 950 mg/day when aged >25 years) [419].

Table 6.1 Vitamin D/Calcium Content Per Food Portion

Fortified Foods	Range	Amount/Portion
Fortified Milk		4µg/200ml
Fortified Yoghurt	0.75-4µg/100g	2.5/100g
Margarine	5-7.5µg/100g	0.75/10g
Yoghurt Drink	1.2-1.7µg/100g	1.5µg/100g
Cheese	2µg/100g	0.4µg/20g
Non-dairy Milk	0.7-0.8µg/100g	0.75µg/100g
Cereals	3.6-8.4µg/100g	3.4µg/40g
Drinking Powder	5-18.4µg/100g	11µg/32g
Slimming Shakes	0.46-0.55µg/100ml	1.6µg/325ml
Oral Nutrition Supplements	2.1-9.3/100g	4µg/55g
Unfortified Foods		
Oily Fish	1.1-16µg/100g	7µg/100g
Offal	0.9-3.3µg/100g	0.5µg/50g
Meat	0.6-1.3µg/100g	0.9µg/100g
Poultry	0-0.3µg/100g	0.25µg/100g
Eggs	3.2µg/2 eggs (110g)	3.5µg/110g
Mushrooms	3µg/100g	2.4µg/80g
Calcium Foods		
Milk	120mg/100ml	240mg/200ml
Yoghurt	200mg/100g	250mg/125g
Bread	106-186/100g	112mg/80g
Cheese	133-739mg/100g	160mg/30g
Breakfast Cereals	30-329mg/100g	42mg/40g
Dark Leafy vegetable	40-216mg/100g	113mg/80g
Nuts/Seeds	170-670mg/100g	74mg/20g
Non-dairy milk	120mg/100ml	240mg/200ml
Small Boned Fish	14-373mg/100g	818mg/85g
Tofu/Soya	350-683mg/100g	478mg/100g

6.3 Results

6.3.1 Demographics

Questionnaires were completed by 383 (32%) of the contacted participants. In 57 cases (4.5%), they were not received by the participant due to a change of address and in 15 (1.1%) were not completed due to death or illness (Figure 6.1). Characteristics of the sample are shown in Table 6.2. The average age was 56.0 ± 16.6 years, 60% were female and 90% were of Caucasian ethnicity. Two thirds (67%) had third level education and one fifth (21%) identified as having a condition that could predispose to lower vitamin D. The majority of the population were overweight or obese (58%), with 36% normal and 7% underweight. Most participants were sunseekers (74%), had a high UV body exposure (81%) and used sunscreen (71%). About 50% (192/383) were taking a vitamin D supplement with precise data on vitamin D content and dosing frequency available in 79% (151/191). For this reason, the sample size (n=338) on which there was estimation of total vitamin D intake and analysis of RDA was smaller (Table 6.4). There was a near equal split between seasons, with 57% of results in winter and 43% in summer. In total, 24% of the population were vitamin D deficient (<30 nmol/L), 29% insufficient (30-50 nmol/L) and 5% had levels >125 nmol/L. The associations between vitamin D status and factors are discussed below and outlined in Table 6.5 and Figure 6.2. A responder analysis was completed and found that non-responders were significantly younger (Mean age 50.6 vs. 56.0 years, $P<0.001$), had lower 25(OH)D (49.9 vs. 57.4 nmol/L, $P=0.002$), and were less likely to be female (53% vs. 60%, $P=0.023$), than responders to the questionnaire.

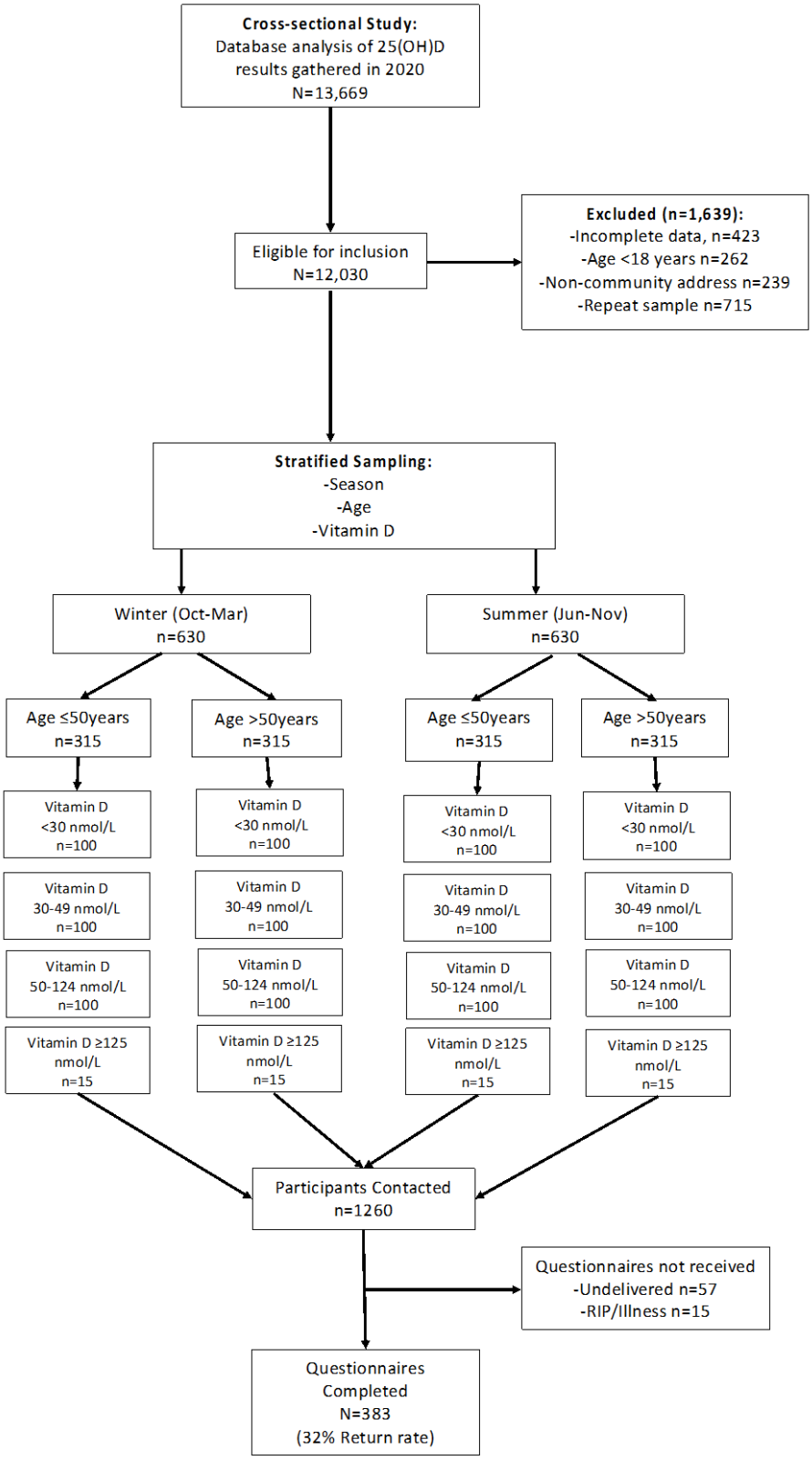


Figure 6.1 Recruitment Flow Diagram

Table 6.2 Population Demographics

		n	%
Sex	Female	230	60
	Male	153	40
Age	<50	145	38
(years)	≥50	238	62
Age Categories	18-39	72	19
(years)	40-49	69	18
	50-59	66	17
	60-69	87	23
	70-79	60	16
	>80	29	8
Season	Winter	219	57
	Summer	164	43
Condition affecting Vitamin D*	Yes	79	21
	No	304	79
Ethnicity	White	344	90
	Non-White	39	10
(n=380) (kg/m^2)	Normal Weight	135	36
	Overweight/Obese	219	58
Education 3rd level of above	Yes	256	68
(n=379)	No	123	32
Smoking	Yes	41	11
(n=379)	No	338	89
Alcohol Consumer	Yes	311	81
	No	72	19
Supplement User	Yes	192	50
	No	191	50
Sunscreen user	Yes	271	71
(n=380)	No	109	29
Sunseeker	Yes	282	74
(n=380)	No	98	26
Body Exposure	Low	73	19
(n=380)	High	307	81
Time spent in peak sunshine	0	74	19
(mins)	<30	64	17
	>30	245	64

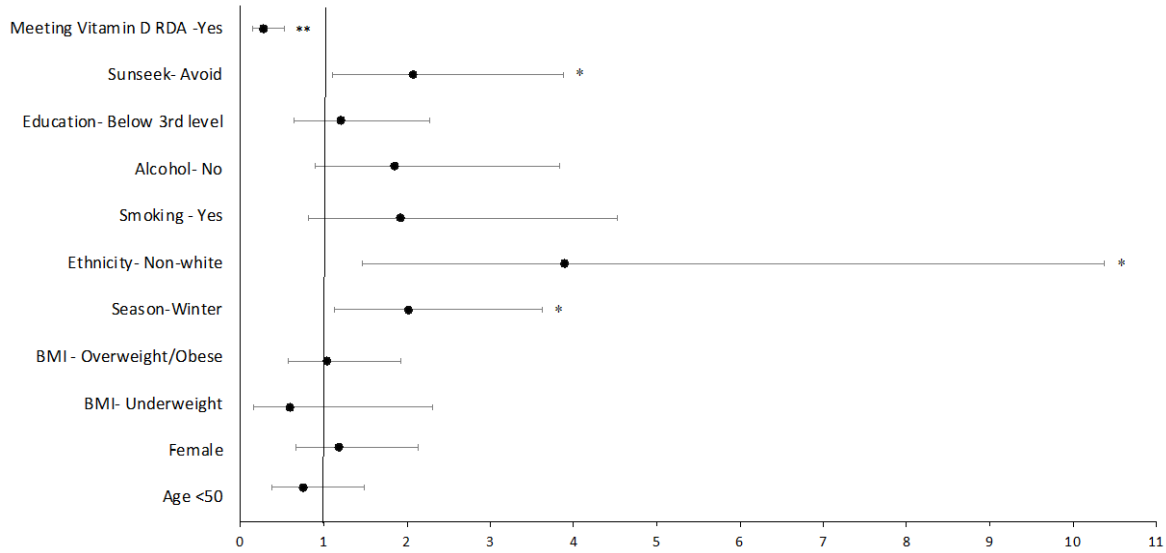
Season: winter; Oct-Mar, summer; Apr-Nov. Conditions affecting vitamin D included; Gut/Gastrointestinal diagnoses e.g. (Crohns Disease, Coeliac Disease, Bowel/Stomach surgery, Inflammatory Bowel Disease), Cystic Fibrosis, Liver/Renal conditions, Pancreatic Disease and Eating Disorders. Body Mass Index was determined based on response to a 10-point image scale [22] on body size categorised as underweight, normal weight, overweight and obese. Sun-seeking was categorised as no (avoid the sun) or yes (spend some time/seek the sun). Body Exposure was categorised as low if only face and hands or higher if additional body parts exposed on a sunny day. Time spent outdoors calculated based on the daily period spent outside between the hours of 1pm and 5pm during March to September.

6.3.2 Biophysical

There was no significant difference in 25(OH)D by sex or age (Table 6.3). However, those of Caucasian ethnicity had significantly higher mean 25(OH)D levels than non-Caucasian (50.8 vs. 28.7 nmol/L, $P<0.001$). They also had a substantially lower prevalence of deficiency (24% vs. 60%, $P=0.001$) and higher rate of sufficiency (47% vs. 20%, $P=0.022$) in winter. In summer, results for Caucasian vs. non-Caucasian were also similar for deficiency (16% vs. 47%, $P=0.001$), and sufficiency (55% vs. 16%, $P=0.001$). Compared to the Caucasian population, the non-Caucasian cohort had a higher proportion <50 years (77% vs. 33%, $P<0.001$) and of non-alcohol consumers (64% vs. 14% $P<0.001$), but there was no difference in supplement use, season of sample, smoking, education, body exposure or proportion meeting vitamin D RDA. Furthermore, being non-Caucasian was an independent predictor of deficiency (OR 3.90 CI 1.46-10.38, $P=0.006$) (Figure 6.2). Vitamin D levels were also lower in those who were overweight or obese vs. normal weight (45.2 vs. 51.2 nmol/L, $P=0.014$) but this was not found to be an independent predictor of deficiency. No significant difference in 25(OH)D was identified between those with or without a condition affecting vitamin D (47.1 vs. 48.2 nmol/L, $P=0.774$).

6.3.3 Lifestyle / Social Factors

There was a trend for a lower overall mean 25(OH)D concentrations in smokers vs. non-smokers (40.0 vs. 49.5 nmol/L, $P=0.065$) though only in winter did they have a higher prevalence of deficiency (43% vs. 23%, $P=0.047$). Furthermore, smoking was not found to predict deficiency when adjusting for other factors. Alcohol users had higher 25(OH)D than non-users (51.3 vs. 35.8 nmol/L, $P<0.001$) and were also less likely to be deficient in winter (23% vs. 50%, $P=0.001$) and summer (14% vs. 37%, $P=0.002$). However, they were also more likely to be sunseekers (78% vs. 58%, $P<0.001$) and it was not identified as an independent predictor of deficiency (Figure 6.2). Finally, those with 3rd level education had higher 25(OH)D (51.3 vs. 42.6 nmol/L, $P=0.018$) and were more likely to have sufficient status in the summer (61% vs. 32%, $P<0.001$) but no relationship was found with deficiency in multivariate analysis.



Binary logistic regression includes reference category for each variable: Meeting Vitamin D RDA; No, Sunseek; Yes, Third Level Education; Yes, Alcohol Consumer; Yes, Smoking; No, Ethnicity; White, Season; Summer, BMI; Normal weight, Sex; Male, Age; ≥50 years. * $P<0.05$, ** $P<0.005$.

Figure 6.2 Independent Predictors of Vitamin D Deficiency in Irish Adults

Table 6.3 Vitamin D Categories by Season

					Winter							Summer						
		n	GM Mean (SD)	*P*-value	n	<30 (%)	*P*-value	30-49 (%)	P-value	≥50 (%)	*P*-value	n	<30 (%)	*P*-value	30-49 (%)	P-value	≥50 (%)	*P*-value
Sex	**Female**	230	48.2 (36.0)	0.853	135	27	0.908	24	0.073	49	0.083	95	21	0.559	33	0.336	46	0.197
	Male	153	47.5 (32.2)		84	27		36		37		69	17		26		57	
Age	**<50 yrs**	145	48.5 (38.3)	0.704	81	30	0.492	26	0.477	44	0.974	64	20	0.836	22	0.703	58	0.140
	≥50 yrs	238	47.6 (31.9)		138	25		30		44		100	19		35		46	
Age Category	**18-39**	72	43.3 (39.1)	0.380	40	40	0.129	25	0.335	35	0.113	32	22 %	0.979	25%	0.372	53 %	0.528
(years)	**40-49**	69	54.0 (37.1)		37	22		24		54		32	19		19		63	
	50-59	66	47.3 (31.4)		43	26		42		33		23	17		26		57	
	60-69	87	50.9 (32.9)		51	16		27		57		36	19		36		44	
	70-79	60	44.0 (34.2)		34	35		21		44		26	23		35		42	
	>80	29	47.9 (27.2)		14	29		36		36		15	13		47		40	
Condition affecting Vit D	**Yes**	79	47.1 (35.1)	0.774	37	38	**0.101**	22	0.292	41	0.614	42	19	0.930	36	0.338	45	0.419
	No	304	48.2 (34.4)		182	25		30		45		122	20		28		52	
Ethnicity	**White**	344	50.8 (34.3)	**<0.001**	199	24	**<0.001**	30	0.364	47	**0.022**	145	16	**0.001**	29	0.461	55	**0.001**
	Non-White	39	28.7 (26.2)		20	60		20		20		19	47		37		16	
BMI	**Underweight**	26	61.2 (35.8)	**0.014**	12	25	0.963	8	0.094	67	0.152	14	14	0.581	21	0.705	64	0.319
(n=380)	**Normal Weight**	135	51.2 (41.5)		83	28		24		48		52	15		29		56	

Table 6.3 Vitamin D Categories by Season Continued

					Winter							Summer						
		n	GM Mean (SD)	*P*-value	n	<30 (%)	*P*-value	30-49 (%)	P-value	≥50 (%)	*P*-value	n	<30 (%)	*P*-value	30-49 (%)	P-value	≥50 (%)	*P*-value
	Overweight/ Obese	219	45.2 (28.2)		122	26		34		40		97	22		32		46	
3rd Level Education	**Yes**	256	51.3 (34.9)	**0.018**	150	23	0.071	32	0.150	45	0.779	106	15	0.072	24	0.02	61	**<0.001**
(n=379)	**No**	123	42.6 (33.1)		67	34		22		43		56	27		41		32	
Smoking	**Yes**	41	40.0 (33.8)	0.065	23	43	**0.047**	35	0.521	22	**0.019**	18	33	0.104	17	0.201	50	0.912
(n=379)	**No**	338	49.5 (34.5)		194	24		28		47		144	17		31		51	
Alcohol Consumer	**Yes**	311	51.3 (34.2)	**<0.001**	185	23	**0.001**	30	0.252	47	0.057	126	14	**0.002**	27	0.14	59	**<0.001**
	No	72	35.8 (33.0)		34	50		21		29		38	37		39		24	
Supplement User	**Yes**	192	60.0 (37.0)	**<0.001**	107	15	**<0.001**	21	**0.009**	64	**<0.001**	85	8	**<0.001**	28	0.634	64	**0.001**
	No	191	38.3 (27.0)		112	38		37		25		79	32		32		36	
Sunscreen user	**Yes**	271	52.5 (36.0)	**<0.001**	157	22	**0.013**	34	0.005	44	0.719	114	13	**0.004**	27	0.223	60	**0.001**
(n=380)	**No**	109	39.4 (27.7)		60	38		15		47		49	33		37		31	
Sunseeker	**Yes**	282	50.6 (35.1)	**0.041**	172	23	**0.019**	31	0.134	46	0.476	110	15	0.095	29	0.697	55	0.095
(n=380)	**No**	98	42.3 (32.1)		45	40		20		40		53	26		32		42	
Body Exposure	**Low**	73	42.4 (32.9)	**0.044**	34	32	0.38	35	0.381	32	0.115	39	31	**0.032**	33	0.609	36	**0.031**
(n=380)	**High**	307	49.8 (34.7)		183	25		28		47		124	15		29		56	
Time spent in peak sunshine	**0**	74	44.8 (34.3)	0.531	41	37	0.225	20	0.131	44	0.840	33	24	0.745	36	0.186	39	0.118
(mins)	**<30**	64	47.3 (37.3)		37	30		22		49		27	19		41		41	

Table 6.3 Vitamin D Categories by Season Continued

				Winter							Summer						
	n	**GM Mean (SD)**	***P*-value**	**n**	**<30 (%)**	***P*-value**	**30-49 (%)**	**P-value**	**≥50 (%)**	***P*-value**	**n**	**<30 (%)**	***P*-value**	**30-49 (%)**	**P-value**	**≥50 (%)**	***P*-value**
>30	245	49.1 (33.9)		141	23		33		43		104	18		25		57	
Total	383	47.9 (34.5)		219	27		29		44		164	20		30		51	

Vitamin D categories reported as % <30 nmol/L, %30-49 nmol/L and % ≥50 nmol/L. GM Mean; Geometric Mean. Winter was defined as October-March, Summer: April to Sept. *P*-values were determined by Mann-Whitney or Kruskal Wallis test for continuous variables, Chi squared was used for categorical, significant at $P<0.05$ (bold).

6.3.4 Dietary Intakes

The overall contribution of diet to vitamin D intake was low with half of all participants consuming less than 4.5 μg (180 IU) per day. There was a trend for better vitamin D status with higher levels of vitamin D intake from either unfortified or fortified sources (Table 6.4). However, total dietary vitamin D intake (combining unfortified and fortified foods) was significantly lower in those who were deficient versus sufficient (4.0 vs. 5.2 μg /day, *P*=0.044). We also identified that those who were over 50, had higher dietary intakes (median 5.4 vs. 3.7 μg/day, *P*<0.001) and were more likely to consume oily fish on a weekly basis (60% vs. 30%, *P*<0.001). However, there was no difference in dietary intake by sex. We also found that the median dietary calcium intake was 658 mg/day and was significantly different by vitamin D status (*P*=0.004): lowest in those with deficiency (527 mg/day) and highest with sufficiency (768 mg/day).

Table 6.4 Vitamin D and Calcium Intake

		Total	**<30 nmol/L**	**30-49 nmol/L**	**≥50 nmol/L**	
	n	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	***P*-value**
Unfortified food	338	1.9 (2.8)	1.6 (2.8)	2.0 (2.6)	2.1 (2.9)	0.118
Fortified food	338	1.9 (4.4)	1.1 (3.6)	2.0 (4.6)	2.3 (5.1)	0.21
Unfortified & fortified	338	4.5 (5.0)	4.0 (4.5)	4.5 (4.4)	5.2 (5.0)	**0.044**
Supplement intake*	151	10.0 (11.4)	9.3 (11.4)	8.6 (11.4)	12.9 (16.4)	**0.032**
Total vitamin D intake	338	8.8 (15.9)	4.9 (8.5)	7.0 (10.4)	14.4 (20.8)	**<0.001**
Calcium Intake	338	658.3 (615.8)	527.1 (636.7)	595.6 (677.3)	767.9 (540.2)	**0.004**

*Supplement intake dose (total cod-liver oil, vitamin D and multivitamin containing vitamin D) available for n=151. *P*-value determined by Kruskal-Wallis test, significant at *P*<0.05 (bold). Values reported as Median intake (Interquartile range) in micrograms for vitamin D and milligrams for calcium.

6.3.5 Sun Exposure

Mean 25(OH)D was significantly lower in winter vs. summer (46.0 vs. 50.7 nmol/L, *P*=0.044). (Table 6.5) and was found to be independent predictor of deficiency in multinomial regression (OR 2.02, CI 1.12-3.63, *P*=0.019). Sunseekers were more likely to have higher 25(OH)D (50.6 vs. 42.3 nmol/L, *P*=0.041) and lower prevalence of deficiency in winter (23% vs. 40%, *P*=0.019). Overall, those who avoided the sun were about twice as likely to be deficient (OR 2.08 CI 1.11-3.88, *P*=0.022) (Figure 6.2). High body exposure was also associated with greater mean 25(OH)D (49.8 vs. 42.4 nmol/L, *P*=0.044) and less deficiency in summer (15% vs. 31%, *P*=0.032). There was no difference in mean 25(OH)D comparing those who spent more or less than 30 minutes in peak sunshine. Finally,

sunscreen users had better 25(OH)D (52.5 vs. 39.4 nmol/L, *P*<0.001) and were less likely to be deficient in winter (22% vs. 38%, *P*=0.013) and summer (13% vs. 33%, *P*=0.004).

6.3.6 Supplement Intakes

The median intake due to supplements was 10.0 μg (400 IU) per day. Higher supplement intake was identified in those who were sufficient versus deficient (median 12.9 vs. 9.3 μg/ day, *P*=0032). Overall, those who took supplements had higher mean 25(OH)D (60.0 vs. 38.3 nmol/L, *P*<0.001) and were much less likely to be deficient in both summer (8% vs. 32%, *P*<0.001) and winter (15% vs. 38%, *P*<0.001). They were also more likely to be sufficient (64% vs. 30%, *P*<0.001).

6.3.7 Total Vitamin D Intake and RDAs

About half of participants and had a total vitamin D intake (diet and supplements) of less than 8.8 μg (352 IU) per day but fewer than 50% of our study sample consumed a supplement. Median total intake was highest in those who were sufficient (14.4 μg /day) and lowest in deficiency (4.9 μg/day). In fact, total intake was twice as high in non-deficient vs. deficient (4.9 vs. 11.1 μg/day, *P*<0.001), and nearly three times higher comparing sufficiency versus non-sufficiency (14.4 vs. 5.8 μg/day, *P*<0.001). Less than half the population (43%) met the vitamin D RDA (Figure 6.3). However, this was much more likely in supplement versus non-supplement users (81% vs. 13%, *P*<0.001). Furthermore, there was a substantially lower prevalence of deficiency (12% vs. 32%, *P*<0.001) and higher sufficiency (64% vs. 33%, *P*<0.001) in those meeting this RDA. Overall, those achieving the RDA were 72% less likely to be deficient (OR 0.28, CI 0.15-0.53, *P*<0.001) (Figure 6.2). We identified that 30% achieved the RDA for dietary calcium intake.

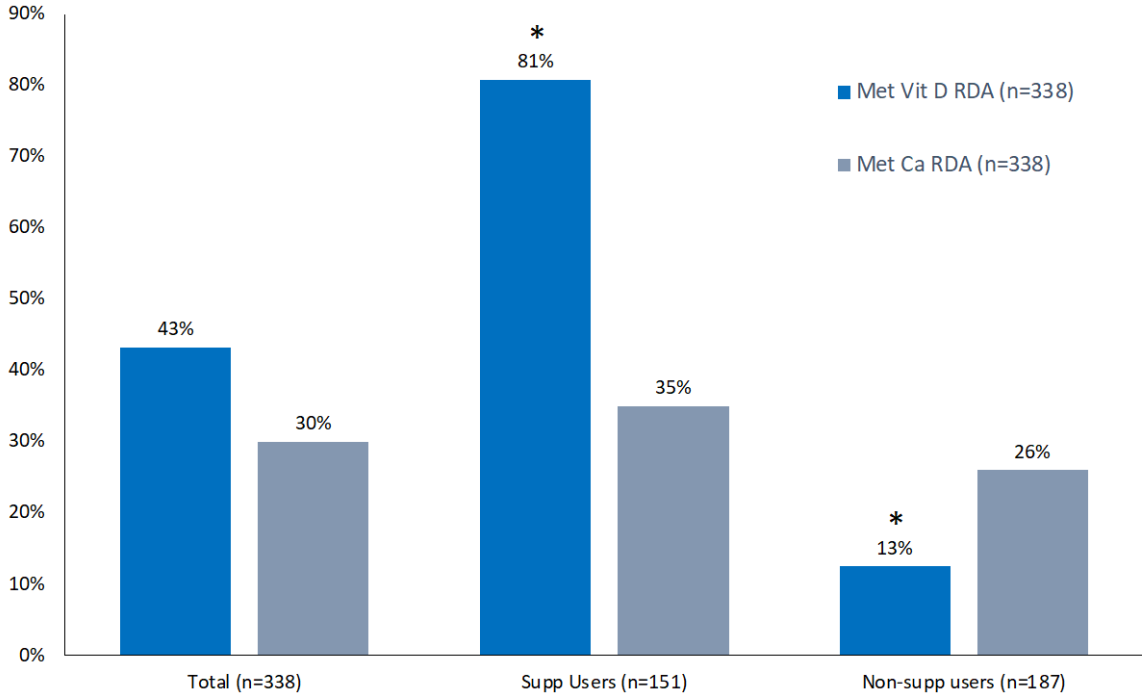
Table 6.5 Vitamin D Categories and Serum 25(OH)D by Season

		Total				Winter			Summer		
		n	**<30**	**30-49**	**≥50**	**n**	**GM Mean (SD)**	***P*-value**	**n**	**GM Mean (SD)**	***P*-value**
Sex	Female	230	24%	28%	48%	135	47.9 (37.4)	0.211	95	48.7 (34.2)	0.266
	Male	153	23%	31%	46%	84	43.1 (30.2)		69	53.5 (33.1)	
Age	<50 yrs	145	26%	24%	50%	81	45.4 (37.8)	0.743	64	52.7 (38.7)	0.366
	≥50 yrs	238	23%	32%	45%	138	46.3 (33.3)		100	49.4 (30.0)	
Age Category	18-39	72	32%	25%	43%	40	38.5 (39.9)	0.065	32	50.1 (37.5)	0.874
(years)	40-49	69	20%	22%	58%	37	52.7 (34.4)		32	55.5 (40.2)	
	50-59	66	23%	36%	41%	43	44.1 (33.3)		23	54.1 (27.3)	
	60-69	87	17%	31%	52%	51	53.9 (35.0)		36	46.9 (29.8)	
	70-79	60	30%	27%	43%	34	41.4 (34.4)		26	48.3 (34.0)	
	>80	29	24%	29%	47%	14	45.2 (25.3)		15	50.7 (29.5)	
Condition affecting Vit D	Yes	79	28%	29%	43%	37	41.4 (26.3)	0.334	42	52.6 (40.2)	0.769
	No	304	23%	29%	48%	182	47.0 (36.4)		122	50.0 (31.3)	
Ethnicity	White	344	20%	29%	50%	199	48.1 (34.9)	**<0.001**	145	54.8 (33.5)	**<0.001**
	Non-White	39	54%	28%	18%	20	29.5 (31.0)		19	27.9 (20.7)	
BMI	Underweight	26	19%	15%	65%	12	53.0 (37.6)	0.478	14	69.1 (34.6)	**0.019**
(n=380)	Normal Weight	135	23%	26%	51%	83	47.8 (43.4)		52	57.2 (38.2)	
	Overweight/ Obese	219	24%	33%	43%	122	44.6 (27.1)		97	46.0 (29.5)	
3rd Level Education	Yes	256	20%	29%	52%	150	47.5 (35.1)	0.571	106	57.2 (33.8)	**0.002**
(n=379)	No	123	31%	31%	38%	67	43.8 (34.9)		56	41.3 (31.1)	
Smoking	Yes	41	39%	27%	34%	23	35.1 (28.3)	**0.021**	18	47.3 (37.9)	0.909

Table 6.5 Vitamin D Categories and Serum 25(OH)D by Season Continued

		Total				Winter			Summer		
		n	**<30**	**30-49**	**≥50**			**n**	**<30**	**30-49**	**≥50**
(n=379)	No	338	21%	30%	49%	194	47.9 (35.4)		144	51.6 (33.3)	
Alcohol Consumer	Yes	311	19%	29%	52%	185	48.3 (35.5)	**0.004**	126	56.0 (31.8)	**0.001**
	No	72	43%	31%	26%	34	35.2 (28.6)		38	36.4 (36.7)	
Supplement User	Yes	192	12%	24%	64%	107	57.7 (38.3)	**<0.001**	85	62.9 (35.3)	**<0.001**
	No	191	36%	35%	30%	112	37.0 (27.0)		79	40.1 (27.0)	
Sunscreen user (n=380)	Yes	271	18%	31%	51%	157	48.5 (36.8)	0.137	114	58.4 (34.1)	**<0.001**
(n=380)	No	109	36%	25%	39%	60	41.1 (28.8)		49	37.4 (26.4)	
Sunseeker	Yes	282	20%	30%	50%	172	48.4 (36.1)	0.067	110	54.2 (33.3)	0.171
(n=380)	No	98	33%	27%	41%	45	39.2 (29.3)		53	45.2 (34.1)	
Body Exposure	Low	73	32%	34%	34%	34	42.1 (32.1)	0.256	39	42.6 (33.9)	0.051
(n=380)	High	307	21%	28%	50%	183	47.1 (35.5)		124	54.1 (33.3)	
Time spent in peak sunshine	0	74	31%	27%	42%	41	44.2 (36.3)	0.755	33	45.6 (31.2)	0.196
(mins)	<30	64	25%	30%	45%	37	48.4 (38.4)		27	45.9 (36.4)	
	>30	245	21%	30%	49%	141	45.9 (33.8)		104	53.8 (33.6)	
	Total	383	24%	29%	47%	219	46.0 (34.9)		164	50.7 (33.7)	**0.044**

Vitamin D categories reported as % <30 nmol/L, % 30-49 nmol/L and % ≥50 nmol/L. GM Mean; Geometric Mean. Winter was defined as October-March, Summer: April to November. *P*-values were determined by Mann-Whitney or Kruskal Wallis test for continuous variables, Chi squared was used for categorical, significant at $P<0.05$ (bold).



Analysis by Chi-square, *significant at *P*<0.001. Supp users; Supplement users, Non-supp; non-supplement users. Vit D; Vitamin D, Ca; Calcium, RDA; Recommended Dietary Allowance. Vitamin D RDA; 10 µg/day, Calcium RDA; 1000 mg/day in those aged 18-24 and 950 mg/day when aged >25 years

Figure 6.3 Dietary Compliance with Vitamin D and Calcium RDA's

6.3.8 Vitamin D Excess

Serum 25(OH)D levels ≥125 nmol/L were identified in 19 respondents and was more likely in those aged <50 years (*P*=0.020) and in supplement users (*P*=0.001). The median total vitamin D intake in those with a level ≥125 nmol/L was 27.5 µg (1100 IU) /day, with the highest intake of 145 µg/day (5800 IU) in a patient with a serum concentration of 131 nmol/L. Overall, no participants met the No Observed Adverse Effects Level (NOAEL) of 250 µg (10,000 IU), with 1.5% (n=5) having an intake above the Tolerable Upper Intake Level (UL) of 100 µg (4000 IU) per day [8]. The highest 25(OH)D level identified in this group was 209 nmol/L, with the highest corrected calcium level at 2.55 nmol/L (Mean 2.35 nmol/L).

6.3.9 Vitamin D Knowledge and Indications for Testing

The primary reason, in more than a third (34%) of patients for testing was for a routine health check. Appropriate reasons for testing included unexplained aches and pains (21%), brittle bones (10%) and limited sun exposure (9%) though 19% reported 'other' which included requests due to patient request (n=13), fatigue (n=7) and immunity/COVID (n=6) (Figure 6.4). There was a lack of awareness of current vitamin D guidelines, with nearly half (46%) not knowing, one third (32%) believing the

RDA was more than 20 µg (1000 IU)/day and just 12% correctly identifying 10-15 µg (400-600 IU) /day (Figure 6.5). The vast majority (86%) of respondents cited vitamin D as being important for bone health with 66% citing immunity/COVID, 47% heart health and 40% mental health (Figure 6.6). A total of 40% (n=152) of referrals were inappropriate, including routine health checks (n=132), patient request (n=13) and fatigue (n=7).

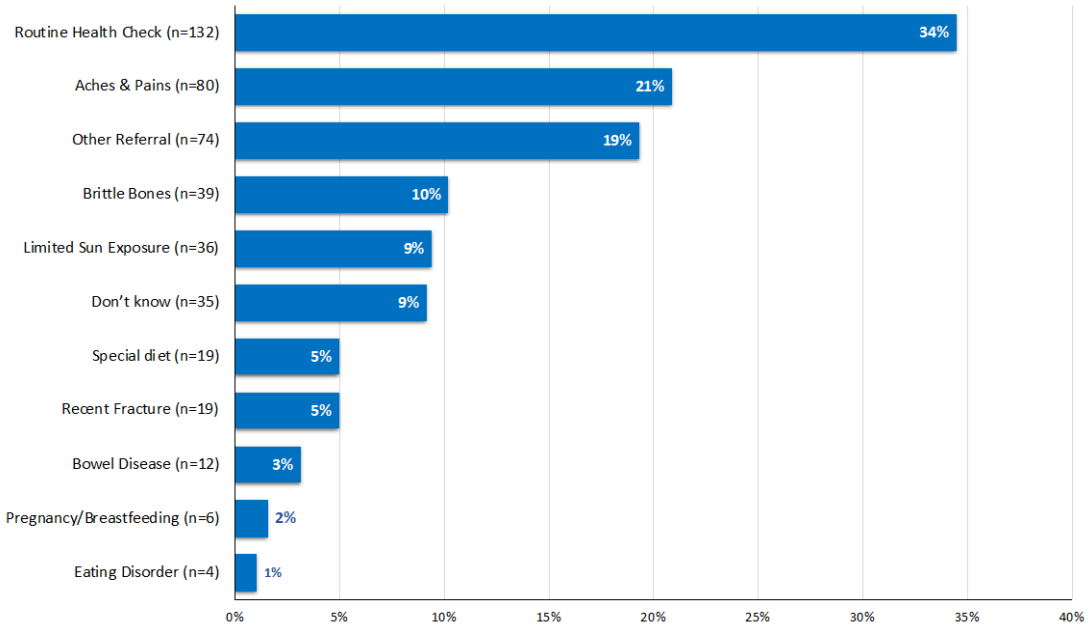


Figure 6.4 Reason for Vitamin D Testing

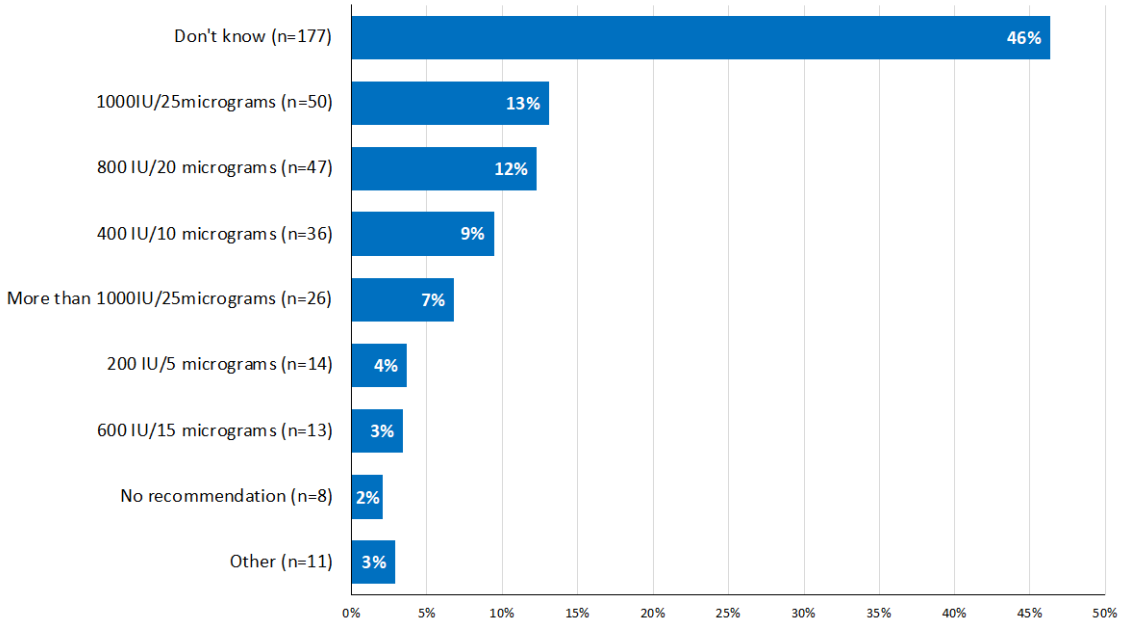


Figure 6.5 Awareness of Vitamin D Recommendations

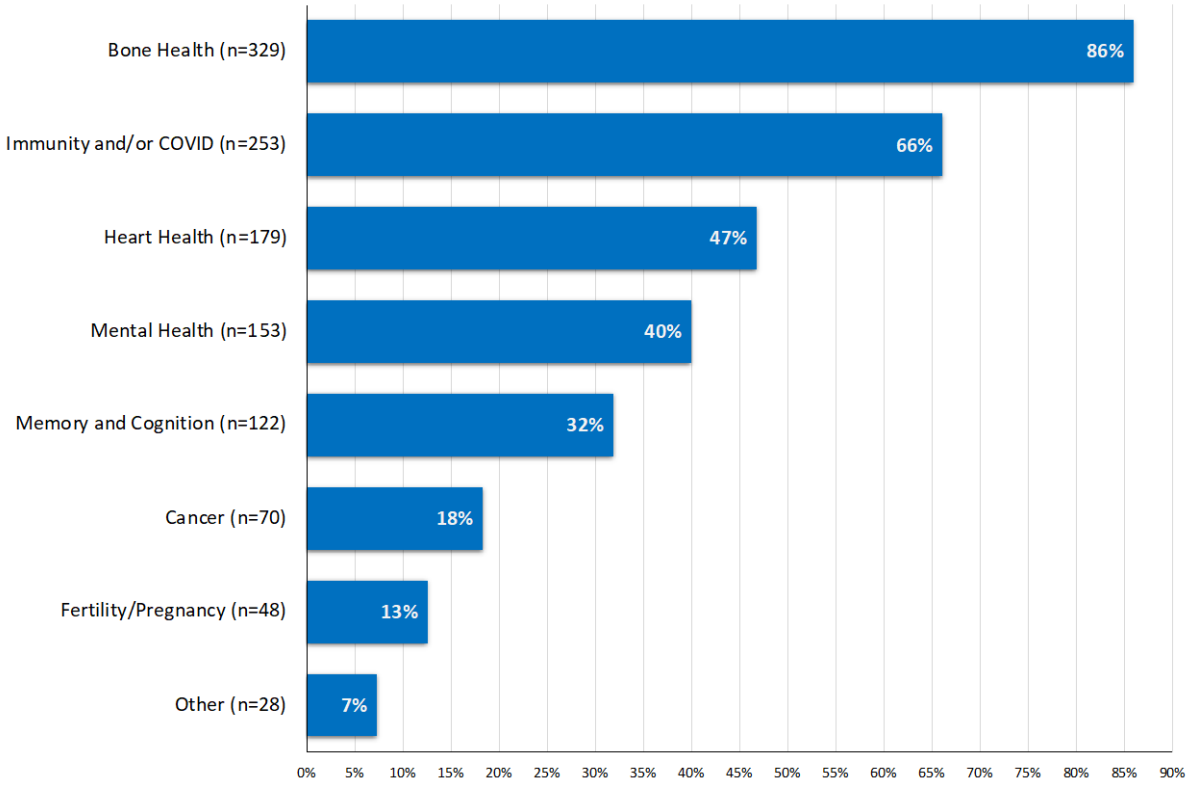


Figure 6.6 Perceptions of Health Conditions Associated with Vitamin D

6.4 Discussion

This is the first study to investigate in detail the determinants of vitamin D status in Irish adults and to explore indications for testing as well as knowledge of vitamin D's role in health and its RDA. The strongest predicators for deficiency were low vitamin D intake (<10 μg/day) and non-Caucasian ethnicity, and it was also twice as likely in sun avoiders and during winter. The contribution of dietary sources to overall intake was small but it was still positively associated with better vitamin D status. However, the vast majority who met the RDA were taking supplements. More than a third had vitamin D testing for inappropriate reasons and less than 12% could correctly identify the recommended dietary intake.

6.4.1 Vitamin D Intake

The overall contribution of diet to vitamin D intake was low with half of all participants consuming less than 4.5 μg (180 IU) per day. However, median total dietary vitamin D intake (combining unfortified and fortified foods) was significantly lower in those who were deficient versus sufficient (4.0 vs. 5.2 μg /day, *P*=0.044). The median intake due to supplements was 10.0 μg (400 IU) per day and those taking supplements were about three times less likely to be deficient in summer. The mean difference in serum 25(OH)D in users versus non-users of supplements was 21.7 nmol/L, which is similar to that found previously in older Irish adults and pregnant women [46, 53, 227]. Older adults had both higher dietary and total vitamin D intakes. These findings are in keeping with other dietary surveys in Ireland that found intakes between 3.0-6.9 μg/day, though being lower in younger (18-35 years) versus older adults (>65 years) [94, 202]. We found similar rates of supplement use by age in this study which contrasts to findings elsewhere [8, 84]. However, oily fish consumption was more frequent in those >50 years in our survey which may partly explain their higher intake.

Nearly half (43%) of adults did not meet the RDA for vitamin D while in those taking supplements this was lower at 19%. However, some supplements, especially those over the counter contain relatively small amounts of vitamin D and /or calcium. Importantly, those achieving the vitamin D RDA were 72% less likely to be deficient though this still occurred in 12% of our population. Previous meta-analysis studies estimated that 12-13 μg/day per day is required for the general population living ≥40°N to maintain wintertime vitamin D status ≥30 nmol/L [201, 420]. However, previous dietary surveys in Ireland have found that just 10% of adults meet the 10 μg/day level, indicating that fortification may be required to achieve adequate vitamin D intakes in the population [84, 201]. In addition, 10% of our survey participants were of non-Caucasian ethnicity, for whom studies suggest require higher vitamin D intakes to optimise status [296]. Furthermore, the RDA (10 μg per day) on

which we based our analysis was the recommendation at the time participants had their serum 25(OH)D tested. However, the Food Safety Authority of Ireland (FSAI) more recently advised on a higher daily intake (15 μg/day) for older adults (aged >65) which constitute 32% of our sample [3]. We found that 1.5% of participants exceeded the UL of 100 μg (4000 IU) per day, but the highest 25(OH)D level identified was below that which predisposes to acute vitamin D toxicity, with no evidence of hypercalcaemia found.

6.4.2 Ethnicity

Non-Caucasian ethnicity was associated with a very high prevalence of winter deficiency of 60% versus only 24% in Caucasian participants. Furthermore, 80% of non-Caucasian ethnicity had insufficient status (<50 nmol/L) in wintertime. There is very limited research on vitamin D status in ethnic populations in Ireland with only four studies published [51-54]. In South-East Asians adults (n=186) living in Dublin, 67% had 25(OH)D <30 nmol/L [51]. A high prevalence of deficiency (<30 nmol/L) was also identified in 81 pregnant women of Middle Eastern and African (88%), Sub-Saharan (68%) and Asian origin (59%) versus 31 indigenous Irish (36%) living in Ireland [52]. A larger study of pregnant woman in Ireland, found that those of non-Caucasian ethnicity had a mean 25(OH)D that was 19.3 nmol/L lower [53]. African ethnicity was also a significant determinant of vitamin D status in a small sample (n=7) of Irish children [54]. We found no difference in vitamin D intake, supplement use, education or body exposure between Caucasian and non-Caucasian participants suggesting that ethnic difference in skin pigmentation is having a dramatic effect on vitamin D status. However, we did not look at sun holiday travel which could explain some of the variation and has been associated with better vitamin D status in older Irish adults [46, 57]. Similar to our study, non-Caucasian ethnicity has been found to predict lower rates of deficiency in England [57] and better vitamin D status in European populations at a similar latitude [291].

In Ireland, about 5% of the population are non-Caucasian and this demographic has increased in recent years [421]. Routine vitamin D supplementation for this section of the population is advisable as it has been found to be more effective than sunlight exposure for treating deficiency [422] and is currently recommended by the European Calcified Tissue Society [50]. Importantly, the vitamin D requirements for non-Caucasians has been estimated to be much higher than the standard RDA advised in Ireland and by most international agencies. For example, maintaining a winter serum 25(OH)D ≥30 nmol/L in 97.5% of individuals who are of South Asian and Black ethnicity would require an estimated respective daily vitamin D intake of 27.3 μg (1092 IU) and 33.2 μg (1328 IU) [296]. Public health information promoting dietary and supplement advice targeting this ethnic population in Ireland may be needed to address this deficiency.

6.4.3 Sun Exposure

We found those who avoided sun exposure were up to twice as likely to be deficient while conversely greater body exposure when outside was associated with higher 25(OH)D concentrations and less deficiency in summer. This is in keeping with other Irish research which found that sun enjoyment was predictive of vitamin D status in older adults [46, 78], and in patients with lupus [183]. Sun-seeking behaviours have been identified as influencing vitamin D status in Irish and European women and children [80, 423]. Our study indicates that summertime deficiency was halved in those with high versus low body exposure. Body exposure (days with sun exposed upper body) has been positively correlated with 25(OH)D at a similar latitude [424]. While there are concerns about skin cancer risk, moderate sun exposure has been shown to make up for deficiency in those who consume relatively low vitamin D [425]. Furthermore, for Caucasian-skinned people in the UK and similar latitudes, spending nine minutes outdoors at lunchtime from March to September was estimated to be sufficient to maintain 25 nmol/L throughout winter [418]. Consistent with this, we found no difference in vitamin D status in those who spent more than 30 minutes in peak sunshine in the same period. We also identified that sunscreen users had better vitamin D status which can be considered a proxy for sun-exposure, with similar findings also reported in the Irish population [54, 139, 426] and at similar European latitudes [427, 428].

Season, as expected, was predictive of vitamin D status, as found in studies of Irish children [54, 137, 140], adults [154, 155], and older adults [43, 48, 153], and elsewhere [57, 163]. In fact, we identified that deficiency was twice as likely in winter. While our study only explored vitamin D status in Dublin, other Irish studies have detected variations in deficiency by geographical location [43] that could be explained by differences in UVB availability due to latitude [78].

6.4.4 Vitamin D Knowledge and Indications for Testing

Despite a surge for vitamin D testing and increasing costs, there remains little evidence on the indications for assessing 25(OH)D status. In a recent Irish study, a high proportion (a third) of vitamin D retests were found to be inappropriate, resulting in considerable unnecessary expenditure, however no information was available on testing indications [15]. In this study, routine health checks accounted for a third of the reasons for testing, though this is not recommended and is considered inappropriate [429]. Additionally, 19% reported other reasons including fatigue which are also not recognised as a valid clinical indication. Our results are similar to the UK and the Netherlands where 70-77% of testing was considered inappropriate [27, 364]. Patient reassurance has also been found to be a key driver of testing by GPs which is consistent with our finding that 'patient requests' were the most frequently declared other reason for testing [364].

We found that half (46%) had no knowledge of any RDA recommendations, though a third (32%) felt it was higher (≥20 μg/day) and 4% lower (≤5 μg/day). Better vitamin D knowledge has been associated with increased likelihood of taking supplements [91], though supplement use has been found to be relatively low (10-17%) in Ireland [43, 84] suggesting a low level of concern for deficiency. However, during the COVID pandemic there is some evidence to suggest increased supplement use in Irish adults and possible improvement in vitamin D status [89]. Indeed, a publicised report by Irish researchers in April 2020 recommended a higher daily vitamin D intake of 20-25 μg (800-1000 IU) during COVID for adults aged >70 [158] so some knowledge of higher RDA's than advised by the FSAI might be expected. The majority (86%) of respondents cited vitamin D as being important for bone health, similar to other studies [91, 430]. Perhaps surprisingly, the second most common health association (66%) was for immunity/COVID. This likely reflects media coverage during the pandemic of research on vitamin D's possible beneficial effects on COVID infection [14]. Indeed, trend analysis indicates there was a peak in Google searches for vitamin D coinciding with the first COVID wave in Ireland (March 2020) and during a subsequent wave (Jan 2021) [431]. The only other research was based on a small sample (n=112) of pregnant women attending a maternity hospital and found that 71% had insufficient knowledge, with just 10% recognising supplements as a source [52]. While there was good awareness of the benefits for bone and immune health, there is poor knowledge of the vitamin D RDA and little understanding of the indications for testing. This suggests that better awareness and may help to improve vitamin D intake and status.

6.4.5 Strengths & Limitations

This is the first study of its kind to explore multiple determinants of serum vitamin D in Irish adults including dietary intake, ethnicity, and measures of sun exposure. It also adds to the limited research on adult knowledge and perceptions of vitamin D in Ireland and is the first to investigate indications for testing. However, as the study participants were selected from a sample of patients who had their vitamin D tested by their GP, it may not be representative of the wider population. Indeed, the respondents to the questionnaire were older, more likely to be female and had higher vitamin D status than non-responders. There may be also exclusion bias given that a significant proportion of adults did not return our questionnaire, though our response rate is in keeping with other studies using a similar methodology [432]. Finally, there may be recall bias as regards the recollection of food and supplement intakes when completing the food frequency questionnaire.

6.5 Conclusion

We found in a cross-section of Irish adults, the biggest predictors of deficiency were low vitamin D intake (<10 μg/day) (P<0.001) and non-Caucasian ethnicity (P=0.006), and was twice as likely in those who were sun-avoiders (P=0.022). In particular, deficiency in winter was nearly four times more likely in those of non-Caucasian ethnicity and was also more prevalent in those with lower body exposure when outside. Dietary sources of intake were small but still associated with better vitamin D status. However, the vast majority (81%) who met the RDA were taking supplements. More than a third of vitamin D testing was for non-clinical indications, and the majority were not aware of the current RDA. Public health policy (including systematic food fortification) should be considered to improve vitamin D intake, especially in those of non-Caucasian ethnicity and with reduced sun exposure.

Chapter 7: Discussion

7.1 Summary of Findings

To the authors knowledge, this is the first time vitamin D research in Ireland has been comprehensively reviewed, it is the largest examination of vitamin D status in the adult population using the novel geomapping tool and an accurate measure of SES in children. It adds to limited evidence of predictors of vitamin D status in adults and is the only to ascertain indications for vitamin D testing, and to explore inappropriate retesting and its costs. The findings of this thesis indicate vitamin D deficiency is highly prevalent in the Irish population, particularly in young adults, adolescents, low SES groups and those of non-Caucasian ethnicity. Testing for non-clinical indications and repeat testing was common, with a high number of these inappropriately referred, at great expense to the health service. While vitamin D intake and awareness of recommendations are low in Irish adults, adherence to the RDA (10 μg/day) was protective of vitamin D status.

As a result of our northern location and limited intake of dietary rich sources of vitamin D, deficiency in the Irish population is common. Societal changes such as increasing obesity, an ageing population and lifestyle habits further reducing vitamin intake and sun exposure may exacerbate this issue. The aims of this thesis were to establish vitamin D status in a large population, and to explore factors contributing to deficiency prevalence. We also investigated the frequency, indications and appropriateness of vitamin D testing, and associated costs.

In Chapter 1, we undertook a literature search of vitamin D research on the island of Ireland, the first of its kind to comprehensively gather the existing evidence to date. It found that several populations are at risk of insufficient vitamin D status, with children, adolescents, younger adults, pregnant women, and ethnic minorities most vulnerable. The seasonal nature of vitamin D production was apparent, with all studies finding inferior status in winter compared to summer. Furthermore, dietary investigations found that every population demographic falls short of meeting recommended intakes, with supplementation levels also found to be low.

The novel tool of geomapping, where laboratory results were combined with location data, was utilised in Chapter 4 to gain a graphical representation of vitamin D status in populations living in Dublin and surrounds. This was the largest study of its kind in Europe, and encompassed data collected over a 5-year period analysed using the gold standard of assessment. Its results were surprising as a population not typically considered to be at-risk of vitamin D deficiency, adults aged

18-39 years, were found to have the lowest vitamin D level in the cohort. Season was found to be the greatest predictor of vitamin D status, with one in four adults found to be deficient in the winter. Furthermore, those living in poorer socioeconomic locations were found to be at increased risk, as were males and those aged over 80 years. This study indicated that large segments of the population in Ireland are at risk of vitamin D deficiency. While previously older women may have been the focus of clinical interventions to improve bone health, this study highlights that other populations, particularly young males in low socioeconomic areas, are at risk and would benefit from increased awareness.

Due to an increased public awareness of vitamin D, requests for blood sampling have increased globally, as well as resulting costs [14]. In Ireland, while this increased demand in vitamin D testing has been observed [16], there has been no previous research on its appropriateness and cost implications. Therefore, in Chapter 4 we aimed to explore the extent of vitamin D testing in Dublin and surrounding counties, and to estimate the associated expenditure. We undertook a retrospective analysis over 5 years of collected serum 25(OH)D data totally over 50,000 sample results. We discovered one in four patients had vitamin D retests during this period. Factors such as female sex, location (Co. Kildare), previous vitamin D status (Deficient <30 nmol/L /insufficient <50 nmol/L) were the strongest determinants of repeat testing. Inappropriate tests were defined as those repeated within 3 months, more than 2 tests within a year and in those patients who were initially replete status. When taken together, the estimated cost of inappropriate tests was calculated at €300,000, or more than €60,000 per year.

Childhood and adolescence are times in which adequate vitamin D is paramount for bone growth and development [87]. As such in Chapter 5, we aimed to gain an understanding of status in children/adolescents age under 18 in Ireland. This study was the largest of its kind to investigate vitamin D in children, and the first to explore its association with a direct measure of socioeconomic status. We found that a quarter of children had low vitamin D status (<30 nmol/L). Socioeconomic status was the strongest determinant of vitamin D status, with more than a third of children living in disadvantaged areas identified as deficient. Furthermore, girls and children over 12 years were also found to be at increased risk as were those who were tested in the winter. These findings are concerning as it indicates that children have higher levels of deficiency and insufficiency than adults.

In Chapter 5, we sought to understand the biophysical, lifestyle and dietary determinants of vitamin D status in the first study of its kind. We found that deficiency in adults is largely determined by

dietary intake, ethnicity, sun habits and season. In addition, while there was understanding of vitamin D's positive relationship with bone health, there was a lack of awareness of supplementation recommendations. Indications for vitamin D testing were also not well understood, with many referred for testing for non-clinical reasons such as routine health checks.

7.2 Public Health Implications

The findings of this thesis indicate that low vitamin D is common in this convenience sample of Irish adults and children. In particular, certain demographics were at increased risk. In adults, it was identified in Chapter 5 that males were at greater risk of deficiency than females. Classically, females have been the focus in terms of bone health, given the increased risk of osteoporosis with ageing. Women typically have more health positive behaviours and are more likely to attend for Primary Health Care [341]. This was confirmed in Chapter 4 at it was found that females were more likely to have a vitamin D retest than males. These findings are concerning, as not only were males more likely to be deficient, but it also indicates that they are tested less frequently and less likely to be followed up. Conversely in children, it was found that females had a higher prevalence of vitamin D deficiency in Chapter 4. This is likely due to greater time spent outdoors undertaking physical activity, less clothing cover and sunscreen use in males compared to females [90, 414, 415]. Similarly, dietary habits of females such as increased likelihood of vegetarianism and veganism may also be playing a role [413].

Given the importance of vitamin D for bone health, there is much research and focus on its effects in older adults. The consequences of low vitamin D in the elderly population are well understood, with increased risk of falls, fractures, and osteoporosis's, and implications for morbidity and mortality [8, 10]. However, in Chapter 3 it was discovered that the youngest adults (18-39 years) were at greatest risk of deficiency, more so than the 'oldest old' (>80y years). This has been attributed to time spent indoors in a working environments and lower intake of supplements [84, 273]. Not only were those age 18-39 years most likely to be deficient, but they were also the least likely to be retested, as found in Chapter 4. As adequate vitamin D status throughout the life course is intrinsic for the maintenance of bone health and the prevention of osteoporosis in later life, the frequency of low vitamin D and the lack of retesting in young adults is concerning. This indicates that not only are they more likely to have low vitamin D status, but they are less likely to be followed up, which may permit inadequate vitamin D levels go untreated leading to consequences for bone, and overall, health. Furthermore, in Chapter 5, vitamin D deficiency was found to be common in children, especially those living in low SES areas. Of particular concern was the finding that older children

(age >12 years), were more likely to be vitamin D deficient than those under 12 years. Childhood, and particularly adolescence, are periods of intensive bone growth, during which demands for vitamin D may be elevated [87]. As peak bone mass is attained in late teens/early twenties, and contributes to lifelong risk of osteoporosis, maintaining adequate vitamin D status is crucial in this age group [387].

Previously it has been identified that in adults those with low socioeconomic status (SES) are at increased risk of low vitamin D due to increased prevalence of obesity, smoking, poorer diet, and lack of access to sun holidays [25, 46-48]. In children (Chapter 5), we identified using a specific measure of socioeconomic status, that those living in poorer areas were twice as likely to be vitamin D deficient than children in affluent areas. A similar finding was identified in Chapter 3, as adults living in areas that have typically lower socioeconomic status, such as West and North Dublin, had much higher levels of vitamin D deficiency. Additionally participant location was predictive of retesting in Chapter 4, with high SES areas such as Co. Kildare more likely, and with those living in North Dublin less likely to be retested. There is a known health disparity between high and low socioeconomic groups, with greater disease burden and poorer life expectancy in those of low socioeconomic status [433]. Hence our findings indicate that low SES populations are more likely to have inadequate vitamin D status and are less likely to be followed up with retesting which is concerning.

To date, there is limited research in Ireland on ethnic populations, which are the fastest growing demographic by latest Census figures [114]. Due to darker skin types, those of non-European descent are at elevated risk of vitamin D deficiency at northern climates than their indigenous counterparts [47]. Therefore, in Chapter 6, we explored ethnicity as a determinant of vitamin D status. We discovered those of non-Caucasian ethnicity were at increased risk of vitamin D deficiency, as found elsewhere [51-54]. Of concern, we found no difference in vitamin D intake, supplement use, education, or body exposure between Caucasian and non-Caucasian groups, indicating skin type is having a pivotal role in vitamin D status. As expected, season a determinant of vitamin D in each of our studies, with significantly lower 25(OH)D status in winter compared to summer in children and adults. In Chapter 6, season and sun habits were predictive of vitamin D deficiency, as those who were sun-avoiders had increased risk of vitamin D deficiency. Furthermore, summertime deficiency was halved in those with high body exposure compared to low. This finding is in keeping with other Irish research that has found sun seeking behaviours/sun enjoyment were positive predictors of vitamin D status. This highlights that despite the variable nature of sun availability in Ireland,

dermal production of vitamin D remains an important factor in the prevention of vitamin D deficiency

Despite our reliance on dietary intake of vitamin D due to low sun exposure, it has previously found to be inadequate in Irish research. As such, in Chapter 6 we aimed to ascertain dietary vitamin D from food and supplements, to examine what proportion were meeting the RDA and to understand whether this was influential on vitamin D status. We found just 43% of the study population met the current RDA of 10 μg/day, with those consuming supplements more likely to reach this level. Furthermore, those who met the RDA were significantly less likely to be vitamin D deficient. Overall vitamin D intake (from food and supplements) was lower in those who were deficient compared to those who had sufficient status. While there was no difference in vitamin D intake by sex or ethnicity, those over 50 years had higher vitamin D intakes than those under 50 years. Those over 50 years were more likely to consume fish weekly and have previously been found to have higher supplement intakes than those under 50 years. This result may partially explain the lower rates of deficiency in this age group as found in Chapter 3.

7.3 Recommendations for Policy

The current recommendations for vitamin D for those aged 12-65 years are to maintain a daily intake of 15 μg (600 IU) from food and supplements [4]. Children aged 0-5 years should be given 5 μg/day (200 IU), with older children (age 6-11) provided with 10 μg/day [1, 2, 4]. Older adults advised to maintain an intake of 15 μg/day (600 IU), increasing up to 20 μg/day (800 IU) if they are housebound with limited sun exposure [3]. Currently there is no increased level recommended for at-risk groups including pregnant women, and ethnic groups. Our research indicates that deficiency is highly prevalent in these demographics, in addition to those with socioeconomic disadvantage. Furthermore, we found that older females were more likely to be tested and retested, despite being less likely to be deficient. Our investigation shows that supplement use and meeting the RDA is predictive of adequate vitamin D status, however recommendations are poorly understood. Our research indicates that just 9% were aware of this recommendation, though 32% overestimated the requirement (>20 μg/day) and 9% underestimated it (<5 μg/day). This lack of awareness of the supplementation recommendations has been found elsewhere, albeit at much lower levels than detected in our analysis [91]. This reflects the need for more guidance, with specific policies necessary to increase uptake and improve vitamin status, particularly in at-risk groups in the population. One method of encouraging awareness of vitamin D is via healthcare professionals (HCP). Previous research in Ireland has found that receiving reminders from an HCP would encourage pregnant

women to eat a diet high in vitamin D [52]. The communication of recommendations around vitamin D during the perinatal period by clinical staff has also been effective in increasing adherence to the infant supplementation policy [101]. Due to the increased contact with HCP's during pregnancy and the first year of life, there is opportunity for education and raising awareness of recommendations [101]. Elsewhere, engagement with a HCP did not improve knowledge, with media cited as the most common source of information, however its accuracy was uncertain [91]. In addition, education on vitamin D and its sources are required. Research in Ireland indicated that while the majority were aware that it can be provided from the sun, 43% incorrectly assumed it could be received from all dairy products, with just 10% selecting supplements as a source [52]. The poor understanding of vitamin D sources other than sunlight, is replicated elsewhere [91]. This highlights the need for dissemination of information to the public to increase knowledge of vitamin D and its sources and to improve awareness of supplementation recommendations.

An alternative method that has been explored elsewhere is the fortification of staple food items. Currently there is a policy of voluntary fortification, with some cereal and dairy products released on the market containing added vitamin D [3]. However, in Finland, the advisory for supplementation and systematic mandatory fortification of fat spreads and dairy products resulted in 91% of the population meeting sufficient vitamin D levels 8 years later [218]. Dietary intakes are currently low, with approximately a quarter of vitamin D intakes coming from fortified sources in Ireland [434]. Our findings are similar, as those with a higher combined unfortified and fortified food intakes were more likely to be sufficient, with no difference in unfortified or fortified intakes alone. While fortified foods form a small but helpful contribution to total intakes, the recommended level was only reached when supplementation was used. This suggests that the current system of fortification is ineffective in preventing deficiency in the population.

In order to identify the correct mode of fortification, numerous modelling studies have explored different possibilities. The fortification of bread and milk products has the potential to allow the majority (70%) of older adults meet the RDA [216]. However, studies in children indicate the consumption of fortified formula, milk and supplements is required to meet adequate levels [211, 212]. Despite the fortification of a variety of foods in Finland, there was no improvement in vitamin D status in young females due to a lack of consumption [331]. As such it is necessary that a comprehensive fortification policy that is achievable for all is implemented so that no aspect of the population is left vulnerable to deficiency.

Current guidance for GPs regarding vitamin D testing does not recommend testing for asymptomatic individuals or routine screening, with no indications on the timing of repeat testing. Our results indicate that vitamin D testing for non-clinical indications, and inappropriate retesting was common and is responsible for significant unnecessary expenditure. Solutions to this issue that have been used elsewhere includes fortification to reduce the need for monitoring or computer systems intervention at the point of ordering to limit unnecessary tests [30, 377]. The latter could involve a centralised system for laboratory ordering of blood tests, connected to medical notes and testing history or requiring predefined criteria to be met. This would limit referrals for 25(OH)D testing to patients who have a clear clinical indication, and within an appropriate time frame. The utilisation of a computer-based strategy has effectively reduced non-essential tests when instigated in other EU countries [359, 380]. While the implementation of an ordering-system for GP's has been recommended by the HSE and would results in significant savings in unnecessary vitamin D testing and repeat tests, this has yet to be rolled-out. As such, updating guidelines for GP's and increasing awareness of the appropriate indications and timescales is possible, but may be ineffective. In addition, as patient requests have been found to be a key driver of vitamin D testing by GPs [373], information directed to the public on deficiency may help curb unrequired referrals

7.4 Strengths and Limitations

Strengths of this research include its novelty, as it is the first to comprehensively review the body of evidence on vitamin D in Ireland to date. It is the largest of its kind to investigate vitamin D in adults using the innovative tool of geomapping, which allowed for an accurate pinpointing of areas of increased deficiency risk. It is one of the largest investigations in children, and the first to explore the effects of social disadvantage using a direct measure of socioeconomic status. In addition, it is the first to ascertain the scale of vitamin D retesting, with respect to its appropriateness and cost implications. Lastly, it is amongst limited studies that have examined the dietary, biophysical and lifestyle determinants of vitamin D in Irish adults, in addition to gathering data on knowledge and awareness. The limitation of the research is that it is not nationally representative, and as such may not be generalisable to the wider population. Additionally, data was collected as part of a convenience sample who had their vitamin D tested, and as such may be subject to selection bias and may not be generalisable to the wider Irish population. Furthermore, data was collected as part of a convenience sample who had their vitamin D tested, and as such may be subject to selection bias.

7.5 Conclusion and Future Directions

The findings of this thesis indicate that vitamin D deficiency is common in children (23%) and adults (15%) in a convenience cross-section of the Irish population. Certain groups such as adolescents, younger adults, and those living in lower socioeconomic areas appear to be at greatest risk of low vitamin D. Determinants of deficiency included having an inadequate vitamin D intake, winter season, sun-avoidant habits, and non-Caucasian ethnicity. Vitamin D testing for non-clinical indications and retesting within inappropriate timeframes was common and contributes to increasing burden on the healthcare system and wasted expenditure. Knowledge of vitamins Ds association with bone health was well understood, however awareness of supplementation recommendations was poor.

Overall, findings indicate there is a lack of data in at-risk populations including those with malabsorption conditions for example Cystic Fibrosis, ethnic minorities, such as non-Europeans and Travellers, and institutionalised adults. To-date there has been no research on vitamin D status in those residing in prisons or emergency/homeless accommodation. Furthermore, while a higher prevalence of inadequate vitamin D was found in children and adults in disadvantaged areas in this thesis, other investigations using a direct measure socioeconomic status are lacking. Thus, future investigations of vitamin D status in vulnerable populations are necessary.

Chapter 8: Value of the Research

8.1 Research Outputs

8.1.1 Publications

Scully H, McCarroll K, Healy M, Walsh J, & Laird E. (2023). Vitamin D intake and status in Ireland: A narrative review. Proceedings of the Nutrition Society, 1-15 (Impact Factor 6.391) https://doi.org/10.1017/S0029665123002185 (Chapter 1)

Scully H, Laird E, Healy M, Crowley V, Walsh J, & McCarroll K. (2023). Vitamin D: Determinants of status, indications for testing and knowledge in a convenience sample of Irish adults. British Journal of Nutrition, 1-11. (Impact Factor: 6.706)
https://doi.org/10.1017/S0007114523000168 (Chapter 6)

Scully H, Laird E, Healy M, Crowley V, Walsh JB, McCarroll K. (2022) Low socioeconomic status predicts vitamin D status in a cross-section of Irish children. Journal of Nutritional Sciences. July 2022. Jul 25;11:e61. (Impact Factor: 3.03)
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https://doi.org/10.3390/nu12092663 (Chapter 3)

Laird E, Walsh JB, Lanham-New S, O'Sullivan M, Kenny RA, **Scully H,** Crowley V, Healy M. (2020) A High Prevalence of Vitamin D Deficiency Observed in an Irish Southeast Asian Population: A Cross-Sectional Observation Study. Nutrients.;12(12):3674. (Impact Factor: 6.706)
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8.1.2 Presentations & Abstracts

Scully, H, McCarroll, K, Healy, M, Crowley, V, Walsh, JB, & Laird, E. (2022). Vitamin D status in Ireland: A review. Nutrition Society Irish Section Meeting June 2022. (Winner of the Postgraduate Research Symposium 2022)

Scully, H., Laird, E., Healy, M., Crowley, V., Walsh, J., & McCarroll, K. (2022). Socioeconomic status predicts vitamin D status in a large cohort of Irish children. Proceedings of the Nutrition Society, 81(OCE4), E87. : https://doi.org/10.1017/S0029665122001161

Johnston D, Byrne F, Scully H, Laird E, Bellew P, Hendrick L, Johnson H, Byrne D, Walsh JB, Healy H, McCartney D. (2022) The association between area-level demographic and socioeconomic parameters and vitamin D status in Ireland. Nutrition Society Irish Section Meeting June 2022. https://doi.org/10.1017/S0029665122001690

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Scully, H., Healy, M., Walsh, J., Crowley, V., McCarroll, K., & Laird, E. (2021). Vitamin D in childhood-high rates of deficiency in a cohort of Irish children. Proceedings of the Nutrition Society, 80(OCE3), E111. https://doi.org/10.1017/S0029665121002342 Presented at Nutrition Society Irish Section Meeting June 2021.

Scully, H., Healy, M., Walsh, J., Crowley, V., McCarroll, K., & Laird, E. (2021). Vitamin D retesting by general practitioners: A factor and cost analysis. Proceedings of the Nutrition Society, 80(OCE3), E112. https://doi.org/10.1017/S0029665121002354. Presented at Nutrition Society Irish Section Meeting June 2021.

Scully H, Laird E, Healy M, McCarroll K, Walsh JB. (2020). Vitamin D deficiency in an older, northern population-the perfect storm on the horizon? Proceedings of the Nutrition Society 79 (OCE2). Presented at Nutrition Society Postgraduate Conference, Dublin, February 2020.

Scully, H., Laird, E., Healy, M., McCarroll, K., & Bernard Walsh, J. (2020). Vitamin D deficiency in an older, northern population - the perfect storm on the horizon? Proceedings of the Nutrition

Society, 79(OCE2), E679. https://doi.org/10.1017/S002966512000628X Presented at Federation of European Nutrition Science Conference, Dublin, October 2019

Scully H, Laird E, Healy M, McCarroll K, Walsh JB. (2019). Vitamin D deficiency in an unfortified northern population. Irish Osteoporosis Society Annual Meeting October 2019

8.1.3 Media (TV/Blogs/Podcast)

Low Vitamin D in Irish Children- *Ireland:AM (31st July 2022)*

The Importance of Vitamin D for Health and Wellness- *Ireland:AM (26th September 2020)*

One in four children in Dublin are vitamin D deficient, study shows - *The Irish Times (July 2022)* https://www.irishtimes.com/health/2022/07/27/one-in-four-children-in-dublin-are-vitamin-d-deficient-study-shows/)

A quarter of all Irish children vitamin D deficient, study shows - *The Independent (July 2022)* https://www.independent.ie/breaking-news/irish-news/a-quarter-of-all-irish-children-vitamin-d-deficient-study-shows-41872094.html)

One in four Irish children vitamin D deficient, study shows - *BreakingNews.ie (July 2022)* https://www.breakingnews.ie/ireland/a-quarter-of-all-irish-children-vitamin-d-deficient-study-shows-1342158.html)

About €300,000 spent on 'unnecessary' vitamin D tests, study finds - *The Irish Times (August 2021)* https://www.irishtimes.com/news/health/about-300-000-spent-on-unnecessary-vitamin-d-tests-study-finds-1.4639139)

'Inappropriate and unnecessary' vitamin D testing carried out, researchers say - *BreakingNews.ie (August 2021)* https://www.breakingnews.ie/ireland/inappropriate-and-unnecessary-vitamin-d-testing-carried-out-researchers-say-1167183.html)

Where you live in Dublin may affect level of vitamin D in your system – study - *The Independent (September 2020)*

https://www.independent.ie/irish-news/where-you-live-in-dublin-may-affect-level-of-vitamin-d-in-your-system-study-39513873.html)

Dublin Vitamin D study shows up to 1/4 of population deficient with younger people worst affected - *Dublin Live (September 2020)*
https://www.dublinlive.ie/news/health/dublin-vitamin-d-study-shows-18912159

The Real Health Podcast: How to boost vitamin D deficiency over winter with nutritionist Helena Scully by Karl Henry.
https://www.independent.ie/podcasts/the-real-health-podcast/the-real-health-podcast-how-to-boost-vitamin-d-deficiency-over-winter-with-nutritionist-helena-scully-39677703.html

Are you getting enough vitamin D – Blog Article by H. Scully
https://rhitrition.com/are-you-getting-enough-vitamin-d/

8.1.4 Professional Communications

Vitamin D: Are we missing the real at-risk groups- *Cover story article in Irish Nutrition & Dietetic Institute- Nutrition and Dietetic Review Magazine* (Winter 2020 Edition)- A PDF of this article can be found in the Appendix Section C, iv.

GP Advisory: the prevalence and determinants of vitamin D deficiency - *Irish Medical Times,* (December 2022)- A PDF of this article can be found in the Appendix Section C, iv.

8.1.5 Policy Reports

Food Safety Authority of Ireland Scientific Committee 'Report on Vitamin D Nutrition for People Aged 5 to 65 Years in Ireland' (February 2023) https://www.fsai.ie/VitD_5-65_14/02/23.aspx

Citation: Scully H, Laird E, Healy M, Walsh JB, Crowley V, McCarroll K. (2020) Geomapping Vitamin D Status in a Large City and Surrounding Population—Exploring the Impact of Location and Demographics Nutrients 12 (9), 2663. https://doi.org/10.3390/nu12092663

Scully, H., Laird, E., Healy, M., Crowley, V., Walsh, J., & McCarroll, K. (2022). Socioeconomic status predicts vitamin D status in a large cohort of Irish children. Proceedings of the Nutrition Society, 81(OCE4), E87. : https://doi.org/10.1017/S0029665122001161

Joint Committee on Health 'Report on Addressing Vitamin D Deficiency as a Public Health Measure in Ireland' (April 2021)
https://data.oireachtas.ie/ie/oireachtas/committee/dail/33/joint_committee_on_health/reports/2021/2021-04-07_report-on-addressing-vitamin-d-deficiency-as-a-public-health-measure-in-ireland_en.pdf

Citation: Scully H, Laird E, Healy M, Walsh JB, Crowley V, McCarroll K. (2020) Geomapping Vitamin D Status in a Large City and Surrounding Population—Exploring the Impact of Location and Demographics Nutrients 12 (9), 2663. https://doi.org/10.3390/nu12092663

Vitamin D COVID Consortium to the Irish Government:
McCartney, D.M., O'Shea, P.M., Faul, J.L. et al. Vitamin D and SARS-CoV-2 infection—evolution of evidence supporting clinical practice and policy development. Ir J Med Sci 190, 1253–1265 (2021). https://doi.org/10.1007/s11845-020-02427-9

Citation: Scully H, Laird E, Healy M, Walsh JB, Crowley V, McCarroll K. (2020) Geomapping Vitamin D Status in a Large City and Surrounding Population—Exploring the Impact of Location and Demographics Nutrients 12 (9), 2663. https://doi.org/10.3390/nu12092663

8.2 Research Impact

These studies represent the largest investigation of vitamin D status completed on the Island of Ireland to date, including a novel review of vitamin D and a detailed analysis of adults and children. Furthermore, analysis of trends in vitamin D testing has not previously been undertaken in an Irish context. This research is also unique in its exploration of contributing factors associated with vitamin D status, utilising focused data collection in the largest questionnaire study based on vitamin D in Ireland. This PhD has gathered data that has great value to many stakeholders, further described below:

8.2.1 Government

This research provides valuable insight to the government regarding vitamin D status in the Irish population. Data on current prevalence of vitamin D deficiency is lacking, particularly in children and adults under the age of 50. The recent onset of the COVID pandemic and the potential role of vitamin D in the severity of this disease has raised the priority in understanding vitamin D status and its implications. The findings from Chapter 3 of this PhD were included as part of an Oireachtas Joint Committee on Health "Report on addressing vitamin D deficiency as a public health measure in Ireland". This report highlighted the depth of the issue of vitamin D deficiency in the Irish population and the role of vitamin D in enhancing public health. As a result, numerous public health measures are being considered to address vitamin D status in Ireland, including clear guidance on vitamin D supplementation, with the suspension of VAT tax to encourage uptake.

8.2.2 Public/Patients

By ascertaining the prevalence of vitamin D deficiency and the scope of the issue in the Irish population, greater targeting of public health measures can be implemented to benefit those most at risk. This will help improve the health of the population, most directly in terms of bone health, but also may reduce the additional consequence of inadequate vitamin D status such as inflammation, brain and heart health and respiratory conditions such as asthma and COVID. This may help prevent long-term deficiency in vulnerable populations and assist them in avoiding the associated ill health effects. The reporting of the findings of these studies will also bring increased awareness on vitamin D and the importance of meeting adequate intakes, via diet and supplementation.

8.2.3 Research/Clinical

This research has enabled the creation of links between the PhD candidate and different academic groups. The research developments described here adds to the knowledgebase of vitamin D and thus encouraged both national and international collaboration in this scientific field. To date, collaborations with two separate research groups within Trinity College Dublin and the Technical University Dublin have been established to share data and enhance understanding on the role of vitamin D in the Irish population. The research has strengthened the candidates' contacts in the field of vitamin D epidemiology and encourage future collaborative projects. The candidate would also be able to develop links with agencies such as the Food Safety Authority Ireland, to examine potential strategies to improve vitamin D status.

This research is also useful to clinicians to raise awareness on the scale of vitamin D deficiency in populations not usually considered to be at risk, such as younger adults. Additionally, investigations on vitamin D testing by Primary Care physicians may help to establish protocols for best practice and clinical indications for retesting. This has the potential to increase efficiency while decreasing needless expenditure to help reduce the ever-increasing burden of inappropriate testing on the health service.

8.2.4 Industry Funders

(Tirlán, Formally Glanbia)

This PhD represents an opportunity to have a philanthropic input into the Irish research community. As this the largest dataset of its kind in Ireland Tirlán benefit from the novel outputs and its association with the project and build its reputation in supporting novel Irish research.

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Appendix

A) Ethics documents

i. LAVID- Ethical Approval Letter and Amendments

Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta
An Academic Partner of Trinity College Dublin

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

Dr Kevin Mc Carroll,
St James's Hospital,
James's Street,
James' Street,
Dublin 8

10th June 2019

REF: Prevalence of Vitamin D Deficiency

REC: 2019-06 Chairman's Action (11)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 22.05.2019
Date of Ethical Review: 05.06.2019
Research and Innovation Application Number: ?

Dear Dr Mc Carroll,

The REC is in receipt of your recent request to TUH/SJH Research Ethics Committee in which you queried ethical approval for the above named study.

The Chairman, Prof. Richard Dean, on behalf of the Research Ethics Committee, has reviewed your correspondence and given **ethical approval** for this study. The following comments were made:

- Please note that the data collected to date which is anonymous and therefore can be used for research. However please note that the process of anonymising now requires consent. Thus only data already collected can be used and any data collected prospectively will need ethical approval and consent.

The following documents were reviewed:

- Cover Letter, dated 22.05.2019

Applicants must submit an annual report for ongoing projects and an end of project report upon completion of the study. It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018. ***Additionally, please note for documents submitted for GDPR purposes that the REC and the Chair are not confirming that you're documents are GDPR compliant, they are approving the document from an ethical perspective.***

Yours sincerely,

Sadhbh O'Neill

REC Officer – Dr Sadhbh O'Neill

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

Dr Helena Scully,
St James's Hospital,
James' Street,
Dublin 8

15th December 2020

REF: LAVID Study

REC: 2020-12 List 47 – Amendment (16)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 17.11.2020
Date of Ethical Review: 11.12.2020

Dear Dr Scully,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the amendment you submitted to the SJH/TUH JREC for the above named study and has given **FULL** approval for this amendment.

The following documents were reviewed:

- *Amendment Request*
- *Amended Application Form*

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Sadhbh O'Neill

_____
REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

ii. EVID- Ethical Approval Letter and Amendments

Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta
An Academic Partner of Trinity College Dublin

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

Ms Helena Scully,
St James's Hospital,
James' Street,
Dublin 8

19th July 2019

REF: THE EVID (Evaluation of Vitamin D) Study

REC: 2019-07 List 27 (18)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 10.07.2019
Date of Ethical Review: 17.07.2019
R&I Application Number: 5658

Dear Ms Scully,

Thank you for your correspondence in which you sent in a response to the Committee's letter which detailed the Committee's queries and concerns in relation to the initial submission for the above referenced research study.

The Chairman, Prof. Richard Dean, on behalf of the Research Ethics Committee, has reviewed your correspondence and has given full approval for your study to proceed. However, the Chair feels that the GP should be contacted as these patients may not be patients of SJH and rather GP blood tests were just sent to SJH.

The following documents were reviewed:

- Email response, dated 10.07.2019
- GP Letter

Applicants must submit an annual report for ongoing projects and an end of project report upon completion of the study. It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018. ***Additionally, please note for documents submitted for GDPR purposes that the REC and the Chair are not confirming that you're documents are GDPR compliant, they are approving the document from an ethical perspective.***

Yours sincerely,

Sadhbh O'Neill

_____
REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Ms Helena Scully
St James Hospital,
James' Street,
Dublin 8

09th March 2020

REF: The Evaluation of Vitamin D (EVID) Study

REC: 2020-02 List 5 – Amendment (21)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 18.02.2020
Date of Ethical Review: 24.02.2020

Dear Ms Scully,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the amendment you submitted to the SJH/TUH JREC for the above named study and has given **FULL** approval for this amendment to proceed.

The following documents were reviewed:

- Amendment Request Form, dated 18.02.2020
- Standard Application Form

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Sadhbh O'Neill

_____
REC Officer – Dr Sadhbh O'Neill

Ms Helena Scully,
St James's Hospital,
James' Street,
Dublin 8

20th August 2020

REF: EVID Study – Evaluation of Vitamin D Study

REC: 2020-07 List 25 – Amendment (30)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 16.06.2020
Date of Ethical Review: 31.07.2020

Dear Ms Scully,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the amendment you submitted to the SJH/TUH JREC for the above named study and has given **FULL** approval for this amendment.
The following documents were reviewed:

- Ethics Amendment Request Form
- Standard Application Form
- Questionnaire

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Sadhbh O'Neill

_____
REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

Dr Helena Scully,
St James's Hospital,
James' Street,
Dublin 8

15th December 2020

REF: EVID Study

REC: 2020-12 List 47 – Amendment (15)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 17.11.2020
Date of Ethical Review: 11.12.2020

Dear Dr Scully,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the amendment you submitted to the SJH/TUH JREC for the above named study and has given **FULL** approval for this amendment.

The following documents were reviewed:

- *Amendment Request*
- *Amended Application Form*

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Sadhbh O'Neill

_____
REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta

An Academic Partner of Trinity College Dublin

Ospidéal San Séamas – Seirbhís Dé agus A Phobail

Research Office

Project ID: 0375

Approval Date: 5 July 2021

Submission Number: 227
Submission Date: 18/06/2021 11:10

Dear Mrs Scully,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that the amendment to your study has received **FULL APPROVAL.** Your study can now proceed.

Study title: EVID -the Evaluation of Vitamin D Study

The following documents were reviewed and approved:

Document Type	File Name	Date	Version
Default	EVID_Amendment_Apr_2021_Signed		
Default	TUH-SJH_REC_Standard_Application_EVID Study_AMENDED APR 2021		

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Ms Chita Murray

Research Ethics & Clinical Trials Manager,

SJH/TUH Joint Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

B) EVID Study documents

i. EVID Study- Consent Form

CONSENT FORM

STUDY TITLE: The EVID Study (Evaluation of Vitamin D Study)

To be completed by the **PARTICIPANT**:

I have read and understood the information leaflet.	YES	NO
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.	YES	NO
I have received enough information about this study.	YES	NO
I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care.	YES	NO
I agree to allow the researchers use my information (personal data) as part of this study as outlined in the information leaflet.	YES	NO
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study	YES	NO
I give my explicit consent to have my data processed as part of this research study'	YES	NO

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES	NO
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES	NO

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

ii. EVID Study- Information Sheet

STUDY TITLE: The EVID Study

(The Evaluation of Vitamin D Study)

Principal Investigator(s):

- Prof JB Walsh, jbwalsh@tcd.ie
- Dr Kevin McCarroll, KMcCarroll@stjames.ie

Co-investigator(s):

- Helena Scully
- Dr Martin Healy
- Dr Eamon Laird

You are being invited to take part in a research study to be carried out at **MISA, St James's Hospital** by Dr Kevin McCarroll. Before you decide whether or not you wish to take part, you should read the information provided in this leaflet carefully. Take time to ask questions – don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. You may wish to discuss it with your family, friends, or GP.

Why is this study being done?

Vitamin D is an important nutrient for bone and muscle health. More recently, it has been found to be important in conditions such as heart disease, depression and inflammatory conditions including diabetes and stroke. Getting enough vitamin D from the diet alone is difficult, yet vitamin D is also produced from sunlight on exposed skin. However, many factors can reduce this process, including the time of year, cloud cover, clothing habits and sun cream use.

In Ireland we were at greater risk of vitamin D deficiency given our poor intakes from food and a lack of sunshine. This is because we are unable to produce vitamin D from sunlight in winter (October-March). In light of its ties to an increased risk of ill-health and early diet, this study plans to see how common Vitamin D deficiency is in a population who have had their vitamin D recently checked at St James Hospital Lab. A random selection of patients will be contacted (via their GP) and invited to complete a 15-minute questionnaire.

Why am I being asked to take part?

You are being asked to take part as you recently had a blood sample referred to St James Laboratory for vitamin D analysis by your GP. By asking you some questions about your diet and lifestyle we want to learn more about why people have the vitamin D status they do.

Do I have to take part? What happens if I say no? Can I withdraw?

You don't have to take part in this study. If you decide not to take part, it won't affect your current or future medical care. You can change your mind about taking part in the study and opt out at any time even if the study has started. If you decide to opt out, it won't affect your current or future medical care. You don't have to give a reason for not taking part or for opting out. If you wish to opt out, please contact Helena Scully, Research Fellow scullyhe@tcd.ie or 01-416 4331 who will be able to organise this for you.

How will the study be carried out?

Patients referred to St James's Laboratory by GPs for vitamin D analysis in 2020 are eligible for inclusion in the study. A random selection of approximately 1000 patients from the St James catchment area will be invited to take part in this study. This questionnaire will be sent to patients addresses, where they can complete it in their own time at their leisure.

What will happen to me if I agree to take part?

The study involves completing a questionnaire on various lifestyle factors (such as diet and time spent outdoors) that are known to affect vitamin D status. This questionnaire is included in the study

pack enclosed with this information sheet. After reading this information sheet, if you wish to be included in the study, please complete the attached consent form. You will also find a copy of the questionnaire to complete, this should approx. 15 minutes. Once you have completed both the consent from and questionnaire, you can return these to the researchers in the stamped addressed envelope provided. If you prefer to complete the consent form and questionnaire online, you will also find a link and QR code for this. Once the consent form and questionnaire are completed, your involvement in the study will end and there is no further follow up. If you do not wish to take part in the study, you do not need to do anything further.

Are there any benefits to me or others if I take part in the study?

By taking part in this study, you can contribute to one of a limited number of studies about Vitamin D and how common deficiency is in the Irish population. While there is no direct benefit to the participant, by learning more about vitamin D deficiency and how it can be avoided, it will help prevent medical conditions associated with deficiency and improve the health of the population.

Are there any risks to me or others if I take part in the study?

There are no risks to taking part in this study.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

Overall study results will be presented in open access peer-reviewed publications, posters, and presentations. No individual results will be made public. No clinical results, advice or treatment management will be provided to participants.

[redacted]

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

Personal data that will be collected as part of this study includes your name, age, and local address, 25(OH)D status, referring GP name and address. Your medical records will not be accessed. Identifiable data is necessary in order to contact participants by their postal address with the questionnaire.

What will happen my personal data?

Arrangements are in place so that personal data will be processed only as is necessary to achieve the objective of the health research and will not be processed in a way that damage or distress will be caused to the participant. Personal data will be kept (in an identifiable format) for the duration of the study (12 months) and will be fully anonymised and archived after this time. The personal data collected as part of this study will not leave the State.

Who will access and use my personal data as part of this study?

The laboratory database will be processed by Dr Martin Healy, Principal Biochemist at St James Lab. The data will be disclosed to Helena Scully will be responsible for processing and control of the data. The data will not leave the St James site and will not be shared outside the EU.

Will my personal data be kept confidential? How will my data be kept safe?

Data collected during the EVID study will be stored in secure, password protected files in St James Hospital. Access will be strictly limited to those who are directly involved in the study. We will allocate a unique reference number to the information you give us, and we will store the information separately from your contact details. This will protect your privacy while allowing the research team – in the unlikely event that some aspect of the data needs to be confirmed or checked - to track back to the information you have provided. When we have finished analysing the information, we will permanently remove the link to the reference number. The information we collect will be published and reported in 'grouped' format – it will be impossible to identify any individual. When the study ends, the grouped data (without any identifying information) will be returned to be archived at St James Hospital.

What is the lawful basis to use my personal data?

The data is being processed under the lawful basis of Article 6, point 1 (e) which states that processing is necessary for the performance of a task carried out in the public interest.

What are my rights?

Under GDPR and Healthy Research Regulations 2018, as a participant of research you have the following rights regarding your data:

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability
- Right to object to profiling

[redacted]

Will it cost me anything if I agree to take part?

No costs will be incurred as part of this study. A stamped addressed envelope has been provided to you to cover the postage cost of the questionnaire return

Who is funding this study? Will the results study be used for commercial purposes?

This study is funded by a grant provided by Glanbia PLC and Mercers Institute of Successful Ageing to St James Hospital Foundation. HS is a Research Fellow partially funded by Glanbia PLC. Glanbia will have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Has this study been approved by a research ethics committee?

This study has been reviewed and approved by the St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee (ResearchEthics@tuh.ie). Ethical approval was granted for this study on 05/07/2021. There are no personal links between the research team and ethics committee. An annual progress report will be submitted to the committee, in addition to reporting of any adverse events.

[redacted]

Will my personal data be used in future studies?

Personal data will not be stored for use in future studies. All data will be anonymised and stored in group format after completion of the study for up to 5 years after which it will be destroyed.

[redacted]

Where can I get further information?

- Principal Investigator(s): Prof JB Walsh, jbwalsh@tcd.ie
- Dr Kevin McCarroll, KMcCarroll@stjames.ie
- Data Controllers: Dr Martin Healy, mhealy@stjames.ie
- Data Processor(s): Helena Scully, scullyhe@tcd.ie, 01-416 4331
- Data Protection Officer: dataprotection@stjames.ie.

What happens if I wish to make a complaint?

Complaints can be directed to St James's Research and Innovation department; Email research@stjames.ie, Phone; (01) 4151978

Will I be contacted again?

Once you have completed and returned the consent and questionnaire, your involvement in the study will end and you will not be further contacted.

EVID Study Questionnaire

iii. EVID Study- Participant Questionnaire

Vitamin D Questionnaire

Welcome to My Survey

Thank you for participating in our survey. Your feedback is important.

* 1. Please confirm the following:

- [ ] I have read and understood the information leaflet
- [ ] I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.
- [ ] I have received enough information about this study.
- [ ] I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care.
- [ ] I agree to allow the researchers use my information (personal data) as part of this study as outlined in the information leaflet.
- [ ] I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study
- [ ] I give my explicit consent to have my data processed as part of this research study.

* 2. Please enter:

Your name:

Date:

Vitamin D Questionnaire

3. How familiar are you with vitamin D?

- ◯ Extremely familiar
- ◯ Very familiar
- ◯ Somewhat familiar
- ◯ Not so familiar
- ◯ Not at all familiar

4. Do think vitamin D is important?

Not at all important | A little important | Extremely important

5. If yes, what you think vitamin D is important for: (choose all that apply)

- ☐ Heart Health
- ☐ Memory and Cognition
- ☐ Bone Health
- ☐ Mental Health
- ☐ Cancer
- ☐ Immunity (e.g. Preventing Infection)
- ☐ Fertility/ Pregnancy
- ☐ COVID
- ☐ Other (please specify)

6. How concerned are you about your vitamin D Level?

Not at all concerned | Somewhat concerned | Very concerned

7. Why did you/your G.P. get your vitamin D checked?

- [ ] Brittle Bones
- [ ] Recent Fracture (within the last 5 years)
- [ ] Aches & Pains
- [ ] Special Diet (E.g. Coeliac, Vegetarian, Vegan)
- [ ] Eating Disorder
- [ ] Limited Sun Exposure
- [ ] Pregnancy/Breastfeeding
- [ ] Bowel Disease
- [ ] Routine Health Check
- [ ] I don't know
- [ ] Other (please specify)

8. Have you been diagnosed with one or more of the following conditions?

- [ ] Brittle Bones
- [ ] Muscle/Bone aches and pains
- [ ] Recent fracture (within the last 5 years)
- [ ] Gut/Gastrointestinal condition (e.g. Crohn's)
- [ ] Coeliac disease
- [ ] Bowel/ Stomach Surgery
- [ ] Inflammatory Bowel Disease
- [ ] Cystic Fibrosis
- [ ] Liver/ Renal Condition
- [ ] Pancreatic Disease
- [ ] COVID
- [ ] Eating Disorder
- [ ] N/A
- [ ] If other, please specify

9. Have you been prescribed vitamin D by your Doctor?

- ◯ No
- ◯ Yes- Combined Vitamin D and Calcium (e.g. Ideous, Calci-chew, cadelius)
- ◯ Yes- Vitamin D only (e.g. Desunin, Altavita)
- ◯ Yes, Other (please specify)

10. How common do think vitamin D deficiency is in Ireland?

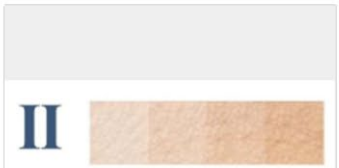
Very Rare — Very Common

11. What do you think is the recommended daily level of vitamin D supplementation in Ireland?

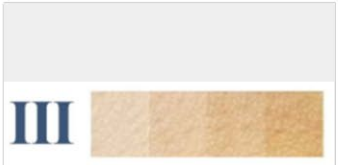
- ◯ No recommendation
- ◯ 200 IU or 5 micrograms
- ◯ 400 IU or 10 micrograms
- ◯ 600 IU or 15 micrograms
- ◯ 800 IU or 20 micrograms
- ◯ 1000IU or 25micrograms
- ◯ More than 1000IU or 25micrograms
- ◯ Don't know
- ◯ Other (please specify)

12. What would you say is your skin type?

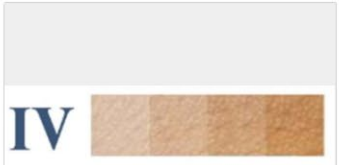
Always burns, never tans



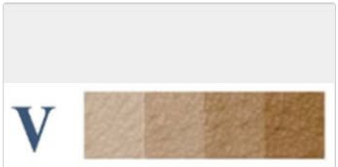
Burns easily, tans minimally.



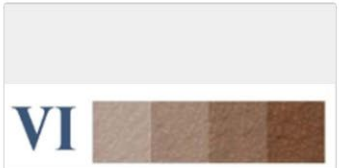
Sometimes mild burn, tans uniformly



Burns minimally, always tans well



Very rarely burns, tans very easily



Never burns

13. What is your ethnicity?

- ◯ White
- ◯ Black
- ◯ Asian - Chinese
- ◯ Asian - Other
- ◯ Other - Including Mixed

14. Between March - September, how many days a week do you typically spend at least 30 minutes outside?

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7

15. Between March - September, how much time do you typically spend outdoors between the hours of;

	No time	15 - 30mins	30mins - 1 hour	1 - 1.5 hours	1.5 - 2 hours
Between 7 and 9am?	◯	◯	◯	◯	◯
Between 9 and 11 am?	◯	◯	◯	◯	◯
Between 11am and 1pm?	◯	◯	◯	◯	◯
Between 1 and 3pm?	◯	◯	◯	◯	◯
Between 3 and 5pm?	◯	◯	◯	◯	◯
Between 5 and 7pm?	◯	◯	◯	◯	◯

16. On a sunny day, do you tend to:

- ◯ Avoid the sun/ seek shade
- ◯ Spend some time in the sun
- ◯ Seek the sun/sun bathe

17. How much skin do you tend to expose on a warm sunny day? Select all that apply

- ☐ None (Stay covered)
- ☐ Face
- ☐ Hands
- ☐ Forearms
- ☐ Full Arms
- ☐ Lower Leg
- ☐ Full Leg
- ☐ Back
- ☐ Chest

18. When you go out in the sun, do you wear sun protection factor (e.g. SPF 15) ?

- ◯ Yes
- ◯ No

If yes, please name the brand and protection factor

19. If you answered yes to Q17, please select how often you would wear sun protection factor when out in sunny weather?

- ◯ Never
- ◯ Seldom
- ◯ About half the time
- ◯ Usually
- ◯ Always
- ◯ Other (please specify)

20. In the last year, how often do you use sun beds?

- ◯ Often (at least once a week)
- ◯ Always (a few times a month)
- ◯ Sometimes (at least once a month)
- ◯ Rarely (a few times a year)
- ◯ Never

21. Do you smoke?

- ◯ Yes
- ◯ No/Not currently

If Yes, please state how many cigarettes per day

22. How often do you consume alcohol on average?

- ◯ Never/ Not in the last year
- ◯ Less than monthly but at least once in the last year
- ◯ 1-3 times a month
- ◯ Once a week
- ◯ 2-3 times a week
- ◯ 4 or more times week

23. How many units of alcohol do you consume per week? (1 unit = 1 small glass of wine OR 1/2 pint of beer/cider OR 1 measure of spirits)

Beer/Cider:

Wine:

Spirits:

24. What is the highest level of education you have completed?

- ◯ Primary or equivalent
- ◯ Intermediate/Junior/Group certificate or equivalent
- ◯ Leaving certificate or equivalent
- ◯ Diploma/Certificate
- ◯ Primary degree
- ◯ Postgraduate/Higher Degree

25. What would best describe your employment type?

- ◯ Unskilled
- ◯ Semi-skilled
- ◯ Non-manual
- ◯ Managerial and Technical
- ◯ Professional
- ◯ Retired
- ◯ Unemployed
- ◯ Other

26. Please select your principal employment status:

- ◯ Employed- Full Time
- ◯ Employed- Part Time
- ◯ Student
- ◯ Retired
- ◯ Unemployed
- ◯ Looking after home/family
- ◯ Illness/Disability
- ◯ Temporary Leave

27. Do you take cod liver oil?

- ◯ Yes, everyday
- ◯ Yes, a few times a week
- ◯ Yes, at least once a week
- ◯ Yes, a few times a month
- ◯ No

If Yes, please state brand used and dose

28. At the time of your blood sample, were you taking a vitamin D supplement?

- ◯ Yes, everyday
- ◯ Yes, a few times a week
- ◯ Yes, at least once a week
- ◯ Yes, a few times a month
- ◯ No

If Yes, please state brand used and dose

29. At the time of your blood sample, were you taking a multivitamin containing vitamin D?

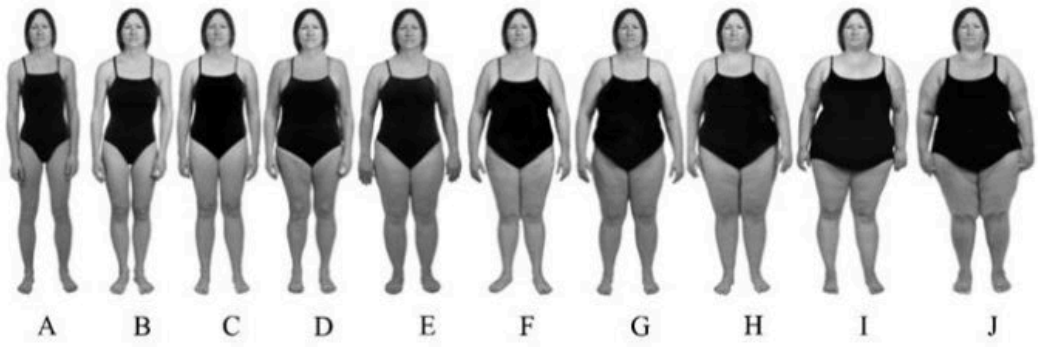
- ◯ Yes, everyday
- ◯ Yes, a few times a week
- ◯ Yes, at least once a week
- ◯ Yes, a few times a month
- ◯ No

If Yes, please state brand used and dose

30. If you know your BMI (Body Mass Index), please select it below:

- ◯ Underweight (Less than 18.5 kg/m2)
- ◯ Normal weight (18.5-24.9 kg/m2)
- ◯ Overweight (25-29.9 kg/m2)
- ◯ Obese (+30 kg/m2)

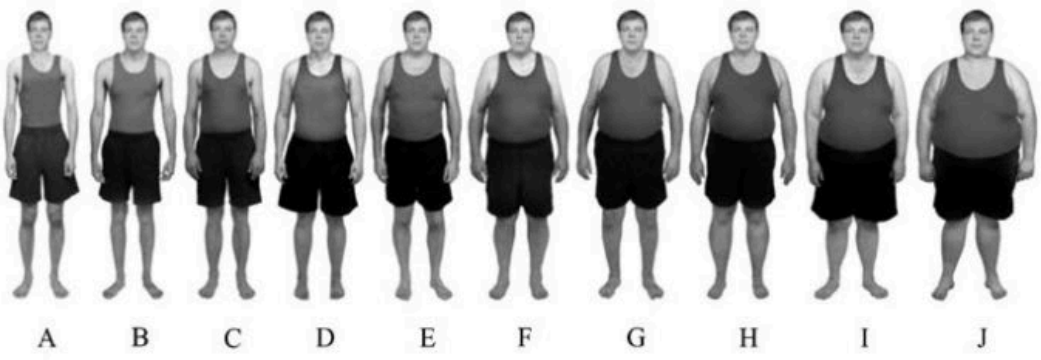
Female Body Size Guide



31. If you identify as female and were to place yourself on the scale above, illustrating various body types, which one do you think closely matches you?

- ◯ A
- ◯ B
- ◯ C
- ◯ D
- ◯ E
- ◯ F
- ◯ G
- ◯ H
- ◯ I
- ◯ J

Male Body Size Guide



32. If you identify as male and were to place yourself on the scale above, illustrating various body types, which one do you think closely matches you?

- ◯ A
- ◯ B
- ◯ C
- ◯ D
- ◯ E
- ◯ F
- ◯ G
- ◯ H
- ◯ I
- ◯ J

33. How often would you consume the following foods that are FORTIFIED with vitamin D?

	Never/ Not Often	1-3 per month	Once a week	2-4 times per week	5-6 times per week	Once a day	2-3 times per day	4-5 times per day
Fortified Milk (e.g. 200ml glass of Supermilk)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Yougurt (e.g. 1 pot/125g of Danone Vitelinea, Yoplait Cal-in, Petite Folous)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Margarine (e.g. Flora, Golden Olive)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Yougurt Drinks (e.g. Actimel /Yakult)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Cheese (e.g. Calvita)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Non-Dairy Milk (Alpro Soya, Oatley)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Breakfast cereals (e.g Kelloggs)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Drink Powders (E.g. Horlicks, Ovaltine, Cadburys drinking chocolate)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Protein Powders (e.g Whey protein)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Slimming Shakes (e.g. SlimFast)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Oral Nutrition Supplements (e.g. Complan, Fortisip)	◯	◯	◯	◯	◯	◯	◯	◯

34. How often would you consume the following foods with natural sources of vitamin D?

	Never/Not Often	1-3 per month	Once a week	2-4 times per week	5-6 times per week	Once a day	2-3 times per day	4-5 times per day
Oily Fish (e.g. 100g of Salmon, Mackerel, Tuna, Sardines, Herring)	◯	◯	◯	◯	◯	◯	◯	◯
Liver or Kidney (e.g. Paté, Lamb liver)	◯	◯	◯	◯	◯	◯	◯	◯
Meat (e.g. 100g of beef, pork, sausages, bacon, lamb)	◯	◯	◯	◯	◯	◯	◯	◯
Poultry (e.g. 100g of chicken, turkey, duck)	◯	◯	◯	◯	◯	◯	◯	◯
Eggs (1 serving = 2 eggs)	◯	◯	◯	◯	◯	◯	◯	◯
Mushrooms (1 serving = 4-5 medium)	◯	◯	◯	◯	◯	◯	◯	◯

35. How often would you consume the following foods with sources of calcium?

	Never/Not Often	1-3 per month	Once a week	2-4 times per week	5-6 times per week	Once a day	2-3 times per day	4-5 times per day
Milk	◯	◯	◯	◯	◯	◯	◯	◯
Yoghurt	◯	◯	◯	◯	◯	◯	◯	◯
Bread	◯	◯	◯	◯	◯	◯	◯	◯
Cheese	◯	◯	◯	◯	◯	◯	◯	◯
Breakfast cereals	◯	◯	◯	◯	◯	◯	◯	◯
Dark Leafy Vegetables (e.g. Broccolli, Cabbage)	◯	◯	◯	◯	◯	◯	◯	◯
Nuts/Seeds (e.g. Brazil Nuts, Almonds, Sesame)	◯	◯	◯	◯	◯	◯	◯	◯
Fortified Non-Dairy Milks (Almond/Soy milk)	◯	◯	◯	◯	◯	◯	◯	◯
Small Boned Fish (e.g Mackerel, Sardines)	◯	◯	◯	◯	◯	◯	◯	◯
Tofu/soya bean curd	◯	◯	◯	◯	◯	◯	◯	◯

Other (please specify food type and frequency)

C) Publications

i. Published Abstracts

Proceedings of the Nutrition Society (2020), **79 (OCE2)**, E679 doi:10.1017/S002966512000628X

The 13th European Nutrition Conference, FENS 2019, was held at the Dublin Convention Centre, 15–18 October 2019

Vitamin D deficiency in an older, northern population - the perfect storm on the horizon?

Helena Scully[1], Eamon Laird[2], Martin Healy[3], Kevin McCarroll[1] and J. Bernard Walsh[1]
[1]*Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin 8, Ireland,*
[2]*School of Medicine, Trinity College Dublin, Dublin 2, Ireland and*
[3]*Department of Biochemistry, St James's Hospital, Dublin 8, Ireland*

Abstract

Introduction: Vitamin D deficiency (VDD) is detrimental to bone health, playing an intrinsic role in osteoporosis and rickets. Recently it has been linked to morbidities including inflammation, cardiovascular disease and cognition. The majority (90%) of vitamin D is obtained by the action of UVB light on the skin, this is reduced in northern latitudes (> 42°N), by SPF, darker skin tone, and ageing. Bioavailability is affected by internal factors including obesity and malabsorption. Many developed populations are becoming older and more overweight. It is essential to ascertain the extent of VDD to predict further trends. The aim of this study is to investigate vitamin D status in a population of GP requested samples within the St James Hospital (SJH) catchment area.

Materials & Methods: The SJH catchment area sits at northerly latitude (53°N) and includes rural and urban environments (Dublin City, Dublin County and County Kildare) of various socioeconomic groups. An estimated 60% of the population are overweight/obese, with 20% aged 65 and over. A data-set of total 25(OH)D concentrations (measured by LC-MS/MS) was created from the SJH laboratory information system from GPs requests between the years 2014–2016. Results were tabulated according to geometric mean values for vitamin D in each postal district with percentage of samples deficient (< 30nmol/L), insufficient (30–50nmol/L), and sufficient (> 50 nmol/L). This data was further stratified by age (18–50, > 50 years) and socioeconomic status and analysed by ANOVA.

Results: A total of 15,483 GP samples were received for vitamin D requests in the time period studied. Preliminary results indicate VDD in 15.2% of the population, with 22.4% insufficient. The lowest socioeconomic areas (Dublin 8 and Lucan postal district) were the most consistently deficient (23.5% and 20.4%, respectively). The geometric mean 25(OH)D concentration in the total population was 56.2nmol/L (SD 31.5), with those age 18–50 years more lively to be deficient than those > 50 years ($P < 0.0001$).

Discussion: This study indicates that VDD remains prevalent across age and location groups at a northern location. Current trends in developed populations, such as the obesity epidemic and ageing populations, may increase rates of deficiency and burden of diseases. With the extent of vitamin D deficiency becoming better understood, its contributing factors require greater evaluation to understand the potential consequences in the population. As such, further analysis and investigations are planned to explore factors contributing to VDD in this cohort.

Conflict of Interest

HS is a Research Fellow funded by Glanbia PLC. Glanbia had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Proceedings of the Nutrition Society (2021), **80 (OCE3)**, E111 doi:10.1017/S0029665121002342

Irish Section Conference, 22–24 June 2021, Nutrition, health and ageing — translating science into practice – Part A

Vitamin D in childhood-high rates of deficiency in a cohort of Irish children

H. Scully[1], M. Healy[3], J.B. Walsh[1], V. Crowley[3], K. McCarroll[1] and E. Laird[1,2]

[1]*Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland,*
[2]*School of Medicine, Trinity College Dublin, Dublin, Ireland and*
[3]*Department of Biochemistry, St James's Hospital, Dublin, Ireland*

Vitamin D is essential in the uptake and metabolism of calcium and is intrinsic for bone health. Childhood/adolescence are periods of intensive bone growth, with vitamin D deficiency causing improper bone mineralisation, resulting in rickets. Recent evidence suggests that the prevalence of rickets is increasing globally[(1)], with levels in the UK the highest seen in five decades[(2)]. Vitamin D intakes have been found to be insufficient (<5ug/day) in up to 94% of 600 Irish children age 5–12 years[(3)], with little recent evidence on vitamin D status. The aim is to assess vitamin D status in a sample of children and adolescents (1–18 years) via a cross sectional analysis of GP requested vitamin D samples analysed at St James's Hospital (SJH).

The SJH catchment area (53°N) includes Dublin City, County and Eastern Leinster. 25(OH)D concentrations (measured by LC-MS/MS) of children age 1–17 years (N = 1,269) between 2014–2020 were analysed. Results were analysed with percentage of deficiency (<30 nmol/L) and insufficiency (30–49 nmol/L). This data was stratified by age (<12 years, >12 years), gender and season (Low; Dec-May vs. High; Jun-Nov), and statistically analysed.

Vitamin D deficiency was highly prevalent in this population with 23% <30 nmol/L and more than half (51%) with insufficient vitamin D status (<50 nmol/L). The geometric mean 25(OH)D was 43.81 nmol/L (SD 25.47). Those over 12 years were more likely to be deficient vs. under 12 years (24% vs. 16%, $p = 0.033$), with girls more likely to be deficient vs. boys (25% vs. 18%, $p = 0.003$). Deficiency and insufficiency were also more common in low season vs. high season (30% vs 16%, $p < 0.001$), (32% vs. 23%, $p < 0.001$, respectively).

Vitamin D deficiency and insufficiency is highly prevalent in this childhood population, with girls, those over 12 years and those assessed in the low vitamin D season most at-risk. These results indicate that low vitamin D status is more common in this childhood cohort versus previously published results in an adult survey of the same population[(4)]. As such, further analysis is planned to explore factors contributing to VDD in this cohort including location, trends in retesting and over time. Poor vitamin D status is common in a large survey of Irish children age 1–17 years, and as such public health measures, including the consideration of a policy for mandatory fortification, should be activated to address this issue.

Acknowledgements

Financial Support: This research is partially funded by Mercers' Institute and Glanbia PLC. Glanbia has no role in study design, data collection and analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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1. Creo AL, Thacher TD, Pettifor J, *et al.* (2017) *Paediatr Int Child Health* **37**(2), 84–98.
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3. IUNA (2019) *National Children's Food Survey II: Summary Report*.
4. Scully H, Laird E, Healy M, *et al.* (2020) *Nutrients* **12**(9), 2663.

Proceedings of the Nutrition Society (2021), **80 (OCE3)**, E112 doi:10.1017/S0029665121002354

Irish Section Conference, 22–24 June 2021, Nutrition, health and ageing — translating science into practice – Part A

Vitamin D retesting by general practitioners: a factor and cost analysis

H. Scully[1], M. Healy[3], J.B. Walsh[1], V. Crowley[3], K. McCarroll[1] and E. Laird[1,2]

[1]*Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland,*
[2]*School of Medicine, Trinity College Dublin, Dublin, Ireland and*
[3]*Department of Biochemistry, St James's Hospital, Dublin, Ireland*

Vitamin D testing by Primary Care doctors is increasing as are the associated costs(1). This places an increased workload on laboratories and healthcare systems though there is little data on vitamin D testing patterns in Ireland. This study aims to investigate the factors associated with vitamin D testing by Irish General Practitioners (GPs) including age, gender and location and resulting costs.

This is a retrospective analysis over 5 years (2014–2018) of GP requested 25-hydroxyvitamin D (25(OH)D) results in 36,458 patients at a major city hospital in Dublin, Ireland. Those with one test were compared with individuals who had follow up testing (retested). Retest samples were categorised to determine changes in status with increasing number of tests.One in four patients (n = 8,305) were retested though all retests accounted for 27.2% of all vitamin D requests. When compared to those not retested, positive predictors of retesting were female gender ($p < 0.001$), age (60–69yrs, $p < 0.001$), location (Co. Kildare, $p < 0.001$) and initial deficiency (<30 nmol/L, $p < 0.001$) or insufficiency (30–49.9 nmol/L, $p < 0.001$). Vitamin D status improved on retesting, halving deficiency on first retest (9% vs. 18%, $p < 0.001$) and dropping to 6% on further retests. 12.2% of retests were done within 3 months, one third (29%) had >2 retests within 1 year and 57% were in those who were initially vitamin D replete (>50 nmol/L). One third (29%) had two or more retests within 1 year. The annual approximate cost of inappropriate testing was estimated at €61,976.

Vitamin D retesting accounted for more than a quarter all requests, varying by age, gender and patient location. One in ten retests were inappropriately early (<3months), a third were too frequent and over half were in replete individuals, incurring significant costs. Clear guidance for GP's on retesting and laboratory ordering systems limiting requests using pre-defined criteria are needed. Population based strategies to reduce deficiency may be more effective than widespread testing.

Acknowledgements

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Irish Section Conference 2022, 15–17 June 2022, Impact of nutrition science to human health: past perspectives and future directions

Socioeconomic status predicts vitamin D status in a large cohort of Irish children

H. Scully[1,2], E. Laird[1,2], M. Healy[1,2], V. Crowley[3], J. B. Walsh[1,2] and K. McCarroll[1]
[1]*Mercers Institute for Research on Ageing, St James's Hospital, Dublin, Ireland,,*
[2]*School of Medicine, Trinity College Dublin, Dublin, Ireland and*
[3]*Department of Biochemistry, St James's Hospital, Dublin, Ireland.*

Vitamin D is essential for bone and muscle health with adequate status in childhood crucial for normal skeletal development [(1)]. Factors related to familial socioeconomic status (SES) have been suggested to affect vitamin D including lower diet quality, reduced intake of oily fish and supplements, and less access to outdoor amenities[(2–4)]. In Ireland, vitamin D synthesis is limited between October and March, as such deficiency is common in adults, with limited research in children. We aimed to investigate vitamin D status in a convenience sample (n = 1,226) of Irish children (aged 1–17 years) who had serum 25-hydroxyvitamin D (25(OH)D) tested by request of their GP at a Dublin Hospital between 2014–2020.A search was completed on 25(OH)D serum results, analysed by liquid chromatography tandem mass spectrometry, at St James's Hospital Biochemistry Department between 2014 and 2020. A sample was identified using the exclusion criteria: age ≥18 years on initial test, incomplete or missing demographic data, non-community address (e.g., Hospital) or location outside the Republic of Ireland. Participant SES was assessed by mapping postal addresses using the 2016 Pobal HP (Haase-Pratschke) Deprivation Index based on the Population Census. We examined vitamin D status and predictors including age, sex, season and SES using Chi2, Kruskal-Wallis and multi-nominal logistic regression analysis. Vitamin D deficiency (<30 nmol/L) was prevalent affecting 23% and was more common in disadvantaged areas (34%) and in those aged >12 versus ≤12 years (24% vs. 16%, P = 0.033).

The greatest predictor was SES (disadvantaged versus affluent, OR 2.18, CI 1.34–3.53, P = 0.002), followed by female sex (OR 1.57, CI 1.15–2.14, P = 0.005) and winter season (October to February, OR 1.40, CI 1.07– 1.84, P = 0.015). More than a half (50.6%) had levels <50 nmol/L, with higher levels in winter versus summer (55.3% vs. 46.9%, P = 0.003). This is the largest study of vitamin D status in Irish children to date. One quarter of our sample were deficient, rising to one third in those in disadvantaged areas. Females, those tested in winter and aged over 12 yrs. had a higher prevalence of deficiency. Public health strategies to improve vitamin D status in Irish children, including systematic food fortification, may need to be considered to address this issue.

Acknowledgments

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Irish Section Conference 2022, 15–17 June 2022, Impact of nutrition science to human health: past perspectives and future directions

The association between area-level demographic and socioeconomic parameters and vitamin D status in Ireland

D. Johnston[1], F. Byrne[1], H. Scully[2], E. Laird[2], P. Bellew[4], L. Hendrick[4], H. Johnson[4], D. Byrne[3,5], J. B. Walsh[2,3], M. Healy[2], V. Crowley[6] and D. McCartney[1]

[1]*School of Biological and Health Sciences, TU Dublin, Dublin, Ireland,*
[2]*Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland,*
[3]*Department of Medical Gerontology, Trinity College Dublin, Ireland,,*
[4]*Health Intelligence Unit, HSE, Dublin, Ireland,*
[5]*Medicine Directorate, St James's Hospital, Dublin, Ireland and*
[6]*Department of Clinical Biochemistry, St James's Hospital, Dublin, Ireland.*

There is an emergent association between vitamin D deficiency (VDD) and the risk of SARS-CoV-2 infection. The prevalence of VDD in Ireland is high,[(1)(2)(3)] particularly in older institutionalised adults[(4)] and low SES groups[(2)] as a consequence of suboptimal sun exposure, inadequate dietary intake, unfavourable lifestyle habits, and low supplementation rates; these same groups are at higher risk of SARS-CoV-2 infection.[(5)] This research project aimed to establish a method for area-level prediction of VDD to aid in the identification of spatial areas at higher risk of VDD which might also be more vulnerable to SARS-CoV-2 infection. This study was a retrospective cross-sectional analysis of area-level vitamin D status amongst community-dwelling adults in Ireland. Serum 25(OH)D concentrations from 7,708 GP-ordered patient samples from counties Dublin, Meath, Wicklow, and North Kildare were derived from the electronic patient database at St James's Hospital, Dublin. These samples were geo-coded by the electoral division (ED) of the residential address using the Health Atlas Ireland/GeoDirectory application. The demographic profile (ethnic mix) and socioeconomic status (the relative Pobal Haase-Pratschke affluence/deprivation score) at the ED level was based on the Census 2016 Small Area Population Statistics (SAPS) published by the Central Statistics Office. The associations between the demographic and socioeconomic parameters and the mean and median ED-level 25(OH)D were examined by univariate (one-way ANOVA with Tukey's *post hoc* multiple comparison test, Kruskal-Wallis with Dunn's *post hoc* multiple comparison test) and multivariate (linear regression, multinomial logistic regression) analyses. There were 412 EDs with indicative 25(OH)D measures. VDD at area-level was defined as mild if the mean ED-level 25(OH)D was 50 - 74 nmol/L, moderate if the mean ED-level 25(OH)D was 30 - 49 nmol/L, or severe if the mean ED-level 25(OH)D was less than 30 nmol/L. ED-level socioeconomic disadvantage was associated with a higher risk of mild, moderate, and severe VDD (OR 1.042 for mild VDD, $p = 0.004$; OR 1.059 for moderate VDD, $p = 0.003$; OR 1.060 for severe VDD, $p = 0.071$ with each one-unit reduction in relative deprivation index score). Each percentage point increment in the prevalence of Asian and Asian Irish ethnicity at ED-level was associated with a higher risk of mild VDD (OR 1.120, $p = 0.041$). Low socioeconomic status and the prevalence of non-white ethnicity at ED-level are predictive of VDD in community-dwelling Irish adults. These findings support the use of area-level population statistics to predict VDD at area-level.

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ii. Published Journal Articles

Chapter 1: Vitamin D in Ireland: a review of existing evidence

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Included in this review is reference to the published study, "A High Prevalence of Vitamin D Deficiency Observed in an Irish South-East Asian Population: A Cross-Sectional Observation Study" Published in Nutrients, Publisher MDPI, IF: 6.706

Citation: Laird, E., Walsh, J. B., Lanham-New, S., O'Sullivan, M., Kenny, R. A., **Scully, H**. & Healy, M. (2020). A high prevalence of vitamin D deficiency observed in an Irish South-East Asian population: a cross-sectional observation study. Nutrients, 12(12), 3674.

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The Nutrition Society Irish Section Postgraduate Conference 2022 was a hybrid event held at the University College Core on 15–17 June 2022

Conference on 'Impact of nutrition science on human health: Past perspective and future directions'
Symposia/Award: Postgraduate Symposium

Vitamin D intake and status in Ireland: a narrative review

Helena Scully[1,2]*, Kevin McCarroll[1,2], Martin Healy[1,2], James Bernard Walsh[1,2] and Eamon Laird[1,2,3]

[1]*Mercers Institute for Research on Ageing, St James's Hospital, Dublin 8, Ireland*
[2]*School of Medicine, Trinity College Dublin, Dublin 2, Ireland*
[3]*Department of Sport and Exercise, University of Limerick, Limerick, Ireland*

Vitamin D is crucial for musculoskeletal health, with evidence suggesting non-skeletal benefits. Cutaneous vitamin D synthesis is limited in Ireland due to its northern latitude (52–55°N) and the population is dependent on dietary sources, yet intakes are inadequate. No study to-date has comprehensively examined vitamin D intakes and status in Ireland (Northern Ireland and the Republic). We aimed to review the evidence since 2010 and summarise the results in subgroups of the Irish population. We found that in the largest studies prevalence of deficiency [25-hydroxyvitamin D (25(OH)D) < 30 nM/l] was 15–17 % in pregnancy, 15–23 % in children and 13 % in adults. Approximately half the population had 25(OH)D < 50 nM/l. There were only four small studies in an ethnic population with the largest in Southeast Asians finding that 67 % were deficient. All studies found higher rates of deficiency and levels <50 nM/l in winter *v.* summer. Vitamin D intake was lowest in children (mean 2·3–4·2 μg/d) and pregnant women (mean 1·9–5·1 μg/d) and highest in older adults (6·9 μg/d), with over 90 % of the population not meeting the recommended daily allowance. This review indicates that low vitamin D status and dietary vitamin D intake are widespread with children, adolescents, younger adults, pregnant women and ethnic minorities most at-risk. However, data are sparse in at-risk groups including the Travelling community, non-Europeans and institutionalised adults. Given the significant prevalence of deficiency, public health policies to promote better awareness of recommended vitamin D intakes and explore the options of food fortification are needed to address this issue.

Vitamin D: Ireland: Childhood: Adults: Ageing

Vitamin D is crucial for musculoskeletal health, being required for the adequate absorption of calcium from the gastrointestinal tract. Vitamin D is a secosteroid synthesised via the action of UVB light on the skin, forming cholecalciferol (vitamin D_3) (Fig. 1)[1]. While this is the predominant physiological source of vitamin D, it can also be obtained from the diet in animal and plant foods (ergocalciferol or vitamin D_2) and from fortified foods[2,3]. Its role in bone health is well established[4], with deficiency increasing the risk of rickets in childhood

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; EU, European Union; TILDA, The Irish longitudinal study on ageing.
***Corresponding author:** Helena Scully, email scullyhe@tcd.ie

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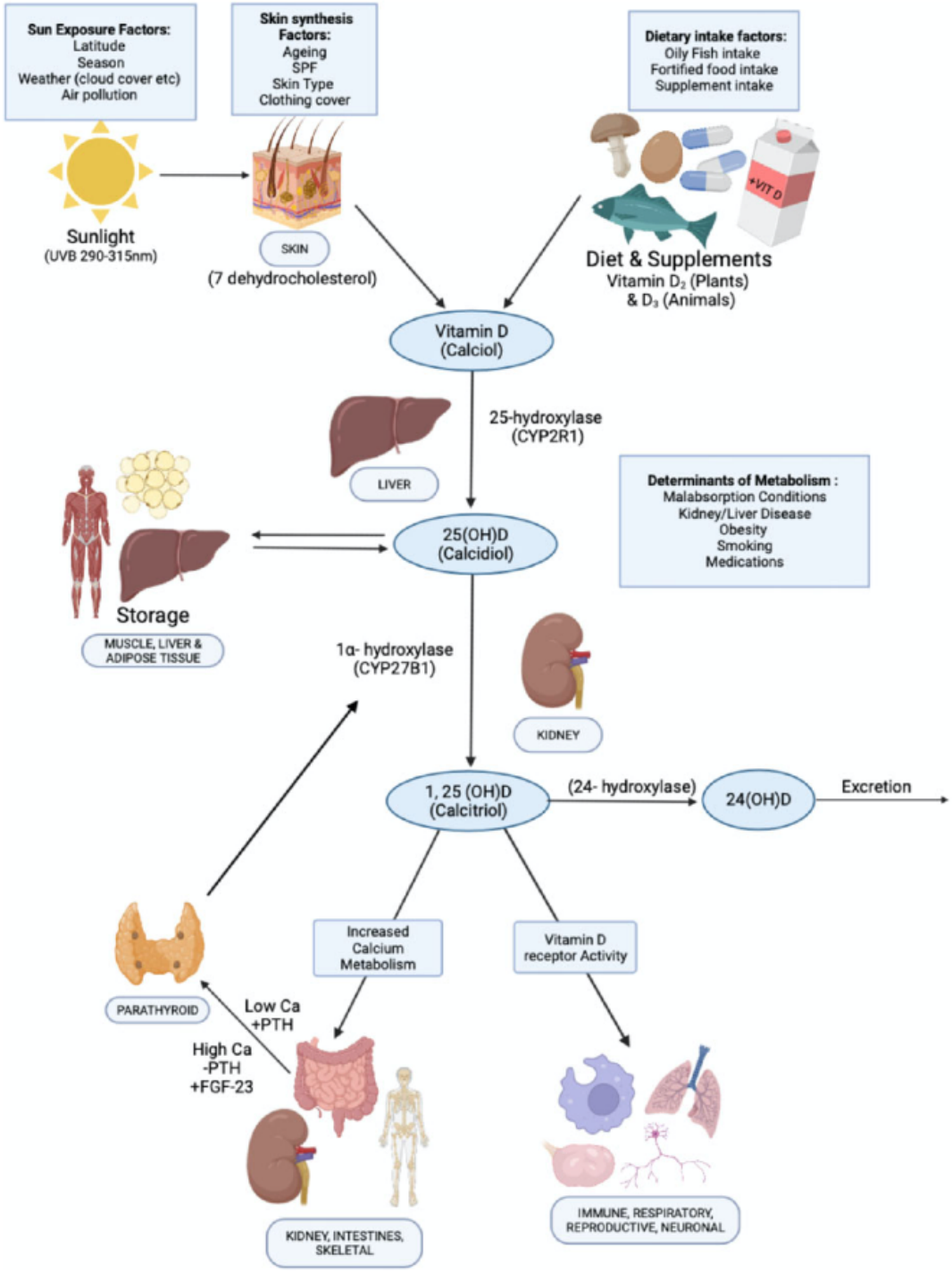

Fig. 1. Vitamin D metabolism. 25(OH)D, 25-hydroxyvitamin D; Ca, calcium; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; SPF, sun protection factor.

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and osteomalacia in adults[1]. Secondary hyperparathyroidism due to vitamin D deficiency can result in musculoskeletal pains and muscle weakness[5]. Peak bone mass, which may determine up to 60 % of osteoporosis risk in later life can only be achieved with sufficient vitamin D and calcium intake[1]. The role of vitamin D may also extend beyond bone health. For example, vitamin D receptors are found in numerous cells including immunological (T- and B-cells), osteoblasts, β cells and mononuclear cells, and in many organs such as the brain, heart, reproductive and the gut[6]. Interaction of transcription factors [1,25-hydroxyvitamin D_2 ($1,25(OH)D_2$)] with the vitamin D receptors modulates gene expression, influencing numerous physiological functions including anti-cancer, immunological and anti-inflammatory effects[7,8]. Thus, it may be involved in the pathogenesis of hypertension, stroke and CVD and may also play a role in immunity, autoimmune diseases, type I and II diabetes, multiple sclerosis, cancer, depression and dementia[6,8–12]. While plausible physiological mechanisms exist for these potential extra-skeletal effects, evidence from robust randomised controlled trials is limited and causality has not been established[4,6]. However, maintaining adequate vitamin D status (>50 nM/l) has been associated with decrease in all-cause mortality in a recent large prospective cohort study[13].

Vitamin D status is determined by a number of intrinsic, environmental and lifestyle factors. Biosynthesis of vitamin D from UVB sunlight (290–315 nm) is dependent on the correct latitude, and for countries above 40°N such as Ireland (52–55°N) this is negligible between October and March[3,14]. Cloud cover, time of day, altitude and air pollution can also affect production and give rise to regional variations in status[15]. Factors including age, skin type, sunscreen use and clothing cover also determines dermal synthesis[16]. Finally, the absorption and bioavailability of vitamin D is affected by malabsorption conditions (e.g. Crohn's/coeliac disease), medication, smoking and obesity[3,17].

As a result of limited sun exposure, the Irish population is dependent on dietary sources of vitamin D, though intakes remain low, and most do not meet the RDA[18]. The RDA as set by the Food Safety Authority of Ireland varies by age as shown in Fig. 2[19–22]. In addition, the proportion at risk of deficiency is rising due to demographic and other changes[20]. For example, the population is ageing, with the proportion over 65 years set to double by 2050[23] and there has also been an increase in those of 'non-white' ethnicity[24]. Levels of overweight and obesity are also on the rise, increasing from 55 and 19 % in 2006 to 61 and 25 %, respectively, in 2016[23]. While there are relatively few cases of rickets, the number reported has increased with twenty-three cases recently described in two Dublin hospitals[20]. For these reasons, knowledge of both trends and current vitamin D status and intake is important in several subgroups of the population.

There is no universal agreement on definitions of deficiency and sufficiency by professional bodies (Table 1). Vitamin D > 125 nM/l is suspected by the National Academy of Medicine as being harmful to health with

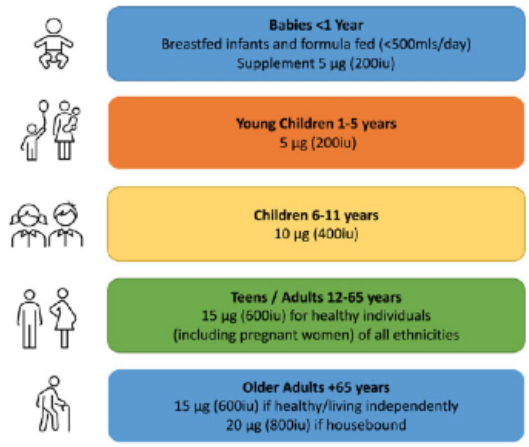

Fig. 2. Irish vitamin D supplement recommendations by age group.

Table 1. Serum 25-hydroxyvitamin D recommendations

Report	Location	Deficiency	Sufficiency
IOM 2011 Report[25]	USA	<30 nM/l	>50 nM/l
Endocrine Society Guidelines 2011[204]	USA	<50 nM/l	>75 nM/l
Nordic Nutritional Recommendations Report 2012[205]	Nordic countries		>50 nM/l
SACN 2016 Report[4]	UK	<25 nM/l	
EFSA 2016 Report[206]	EU		>50 nM/l

potential negative effects on falls, depression and possibly other outcomes including cancer and all-cause mortality in some studies[25–27]. However, the National Academy of Medicine takes a precautionary approach that also factors in ethnic/genetic differences so as to maximise public health protection[27]. Despite this, overt vitamin D toxicity causing hypercalcaemia is rare and usually occurs at levels above 375 nM/l[4,28].

Due to the limited half-life of the biologically active 1,25(OH)D (4–6 h) and its tight feedback control, vitamin D status is assessed by monitoring concentrations of 25(OH)D (half-life 3–4 weeks) which is under no feedback regulation[29]. There are several types of vitamin D analytical techniques, with varying sensitivities and specifications[30]. These include binding assays; RIA, chemiluminescence immunoassay, protein-binding assay, and bioanalytical assays such as HPLC and liquid chromatography tandem mass-spectrometry (LC-MS/MS). Binding assays are relatively quick and inexpensive but are subject to interference from other vitamin D metabolites and may overestimate 25-hydroxyvitamin D [25(OH)D] concentration[29]. HPLC and LC-MS/MS allows for the quantification of a large number of samples, but require more technical skill[30]. LC-MS/MS is now considered the gold standard of vitamin D assessment and

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allows for the measurement of both 25(OH)D_2 and 25(OH)D_3[29]. The vitamin D standardisation programme and vitamin D external quality assessment scheme were developed to improve the accuracy and repeatability of vitamin D assessments[31,32]. Vitamin D intake is typically assessed with FFQ that include 24-h re-calls and 3–7-d food diaries. Weighed food diaries are most commonly utilised in Irish national nutrition surveys and calculate vitamin D intake using nutrient composition databases[33].

To date, no study has comprehensively reviewed vitamin D research with regards to vitamin D status and intakes on the island of Ireland. We aim to summarise the peer-reviewed studies and official reports published since 2010 or earlier for specific sub-groups where no other data was available. For the purpose of this review, we defined deficiency as <30 nM/l and excess as >125 nM/l unless otherwise stated[25].

Vitamin D status and intake by population categories

Pregnancy and fertility

The largest Irish study (*n* 1768) in pregnant women found a prevalence of deficiency of 17 %[34], which was similar to other large studies where it ranged between 15 and 17 %[35,36]. In other studies, it varied between 13 and 65 % but sample sizes were small and were not likely to be representative[37–40]. In general, deficiency was less prevalent in early pregnancy (13–29 %)[34,36–38,41–47] with rates increasing with gestation in most studies[41,42,45,47]. A high proportion of mothers (25–65 %) were also found to be deficient at delivery[39,40]. As expected, a seasonal variation in vitamin D deficiency in pregnancy was found[34,38,43,45,48–50], with the lowest prevalence of 3–7 % detected in summer/autumn[34,38].

The prevalence of levels <50 nM/l in the largest studies were between 42 and 44 %[34–36], while in smaller studies variance was pronounced (44–91 %)[38,40]. A seasonal effect was also evident, with prevalence generally higher in winter *v.* summer[34,38,45,48]. Prevalence of levels below <50 nM/l is similar to some pregnancy studies in Northern Europe where it affected approximately 50 % in the UK[51] and Belgium[52]. Only one Irish study (*n* 138) looked at men and women undergoing fertility treatments and found that one out of five was deficient[53].

Dietary and supplement intakes in pregnancy. Dietary intakes in pregnant women ranged between 1·9 and 10·7 μg/d[46,54], with 80–99 % not meeting the recommendations[54–56]. By comparison, in the UK, 98–100 % were found not to meeting the advised intake of 10 μg/d[57]. In Ireland the RDA in pregnancy is no different from the general adult population at 15 μg/d[22]. However, evidence suggests that pregnant women require 20 μg/d to meet sufficiency (>50 nM/l)[58] with 10–15 μg/d advised by a European consortium[59]. In Finland, the 2003 food fortification of liquid milk resulted in a significant increase in vitamin D intakes in pregnant women[60], and as such should be considered as a public health measure to improve vitamin D status in Ireland.

Nearly 40 % of pregnant Irish women reported taking a specific vitamin D supplement in a Dublin study (*n* 175) in 2016, though the sample was from a confined area[61]. However, when including a multivitamin containing vitamin D, 74·3 % were actually taking some form of supplementary vitamin D[61]. Importantly, less supplement use in pregnancy has been associated with an increased risk of low vitamin D status in Irish infants[49]. Supplementation in Irish pregnant women was also the strongest predictor of 25(OH)D > 30 nM/l with Caucasian females more likely to supplement than those of other ethnicities[37].

Children/adolescents

In the largest study to date (*n* 5524), 15 % of children (5–19 years) were deficient[62], while the second largest (*n* 1226) found a deficiency rate of 23 %[63], though both were conducted in the Dublin area. In most studies deficiency prevalence varied between 5 and 23 %[62–68]. The most recent nationally representative study that measured vitamin D levels in teenagers (aged 13-18 years) found that 21.7 % were deficient though sample size was small (*n*=246)[69]. The highest prevalence of deficiency (63–68 %) was reported in adolescents (aged 12 or 15 years) in Northern Ireland[70]. However, vitamin D was assessed over 20 years ago, was not checked in the months of July or August and the study population was derived after stratified sampling so may not be more broadly representative. Furthermore, the results are discordant with other studies. As expected, the prevalence of deficiency was lower in the summer[66,71,72] and higher in winter when it affected 18–30 % of teens[71,72], and 26 % of children aged 1–17[63]. In general, female children also had lower vitamin D status[63,65,70,73,74], but not in all studies[64].

Notably, there was a 'U-shaped' relationship between deficiency prevalence and age, being lower in younger children (1–12 years) and greatest in adolescents and older children (>12 years)[62,63,65]. For example, a recent large study found a greater prevalence of deficiency in over *v.* under 12s (24 *v.* 16 %)[63]. Lower rates of deficiency (2 %) have been found in toddlers (aged 2 years) and children under 5 (13 %)[64,66], with higher 25(OH)D also reported in those under *v.* over 4 years (61·0 *v.* 46·1 nM/l, $P < 0{\cdot}001$)[65]. Similarly, in a recent large study, deficiency was lower (5 %) in toddlers (1–4 years) but much higher (15·4 %) in older children (5–19 years)[62]. Better vitamin D status in younger children (<5 years) may relate to Ireland's infant supplementation policy[75]. Conversely, lower rates of supplements and fortified food consumption has also been found in Irish teens compared to younger children[76]. One study also reported that older teens (15–18 years) had lower mean 25(OH)D and were more likely to be deficient than younger teens (13–15 years)[69]. Greater screen time/sedentary behaviour and increased obesity rates in this age group may be important factors[77–79]. Socioeconomic status may also explain some of this variation as it has been associated

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with a higher prevalence of deficiency in Irish children[63]. Overall, reports are broadly consistent with findings in northern European countries (47–69°N)[80–83] and in the UK 19 % of 11–18-year-olds were deficient, compared to just 2 % of those aged 4–10[84].

Despite in general, less deficiency in younger children, this was not apparent for those aged <1 year. For example, deficiency in new-borns was high ranging from 34 to 63 % (based on cord blood samples)[35,39,42,49] while in preterm infants 64 % were deficient at delivery[40].

Overall, approximately half of children aged 1–17 years had levels <50 nM/l[62,63,65,68,69], with a seasonal variation identified[63,66,73], similar to findings in the European Union (EU)[75,80–85]. Similar to deficiency, prevalence was lower in younger children (1–5 years), at 21–39 %[62,64,66], and higher in teens at 36–89 % as in UK studies[81]. The prevalence of 25(OH)D < 50 nM/l in new-born cord blood was particularly high (between 80 and 92 %)[35,39,42,49], and similar (79–92 %) in preterm and term infants[35,40,42,44,49].

Dietary and supplement intakes in children. The first nationally representative dietary survey in 2010/2011 in Irish children aged 12–59 months found that 70–84 % had intakes <5 μg/d (mean of 3·2 μg/d)[86]. In a small study (*n* 97) of 5-year-olds in 2019, intake remained low with just 6·2 % having consuming above 5 μg/d[64]. Recent nationally representative surveys of older children (5–12 years) and teens (13–17 years) found the majority (94 %) had intakes <10 μg/d, with little improvement between 2003/2004 and 2017/2018[78,87,88]. In fact, comparing surveys, intakes had improved only a little, from 2·7 to 3·7 μg/d for teens and from 2·3 to 4·2 μg/d for children[87,89–91]. Similarly, in a recent nationally representative study of teenagers (aged 13-18) median intake was 2.9 μg/d[69].

In Irish infants, milk/formula comprised of 29 % of total intakes[86], similar to that in UK children aged 12–18 months[92]. Milk/products were also the greatest source of vitamin D in children <4 years in Ireland followed by meat and its products as found in the UK[86,92]. However, in Irish children aged 5–12 years, fortified cereals were the largest contributor, followed by meat and then milk products[87] as also identified in Belgium and the UK[81,93]. Meat and its products also account for the primary source of vitamin D in Irish children over 13[78,94], despite its relatively low content. This is also reflected in the UK, where it comprised of 35 % of dietary vitamin D intake[4].

Children aged 1–5 years in Ireland are recommended to receive 5 μg/d, supplementing if necessary, with older children (aged 6-11 years) advised to consume 10 μg/d[20,22]. Overall, supplements are an important contributor to vitamin D status in children and adolescents in Ireland[65,95], as found elsewhere in Europe[96–98]. The most recent national dietary survey (2017/2018) of Irish children aged 5–12 years indicated that just 10 % consume a vitamin D supplement[87] which compares to 17 % in a representative sample (aged 1–4 years)[95]. Supplement use has also been found to decrease with age, with 21 % of 5–8, 16 % of 9–12 and 15 % of 13–17-year-olds consuming a vitamin D containing supplement[65,66,76,95]. Similar findings have been reported in the UK, with higher supplementation rates in younger children (14–16 %) compared to teens (5–6 %)[57]. Indeed, since the introduction of an infant supplementation policy in Ireland, initiation of a 5 μg/d supplement from birth increased to 92 %, with 30 % of parents compliant during the first year[99]. In one study, supplement use was reported in 23 % of Irish children (aged 1–17) attending hospital though this could be due to underlying medical reasons[65].

Adults (<50 years)

The largest study (*n* 63 290) revealed that 13 % of Irish adults (<50 years) were deficient between 2020 and 2021[62]. In a nationally representative study, deficiency affected 7 % whereas it was much more common (38 %) in hospital-based inpatients with COVID[18,100]. Deficiency was also more prevalent in younger adults and in winter[101–103]. In Dublin (53°N), between 25 and 30 % were deficient[104,105], though there was a lower prevalence of 10–11 % (<25 nM/l) at a similar latitude in the west of Ireland[106]. In Coleraine (55°N, Northern Ireland) there was a wide variation in deficiency (2–23 %) and in two studies it affected only 0–2 %, though sample sizes in all were small (*n* < 100)[72,107–109]. Overall, deficiency in Ireland appears similar to other European countries[4,59,81,110–112].

Despite not generally being considered an 'at-risk' group, studies indicate that deficiency is more prevalent in younger *v.* older adults (>50 years)[62,100–104,113]. For example, 18 % of younger adults (aged 18–39) *v.* 15 % (aged 40–49) were deficient[101,114]. In addition, urban dwelling younger adults had higher levels of deficiency (<25 nM/l) than rural ones[113]. This nadir in younger adults has also been reported in Romania[115], Canada[116], the USA[117] and Brazil[118]. Lack of sunshine exposure due to time spent indoors in a working environment and reduced dietary and supplementary intakes of vitamin D may be factors[18,94,119].

Levels <50 nM/l were found in more than half of adults living in Dublin[104,105] and 44 % in those living in the West[106]. In several locations across Ireland, a similar prevalence (40–55 %) was also identified[18,120]. In younger Irish adults (aged 18–39) nearly half (45 %) had levels <50 nM/l[101,114] and up to 58 % had <50 nM/l in winter[72,101–103], with this proportion being higher in Cork[72] and Dublin[101–103]. Indeed, studies showed higher rates of deficiency and levels <50 nM/l in winter in Irish adults aged under 50[101,102,113] consistent with findings in the UK[4]. By comparison, in the EU, 34–64 % of adults under 65 had 25(OH)D < 50 nM/l[81,111,121,122].

In general, Irish females had higher 25(OH)D than males[62,101,102,106,113,114] though are twice as likely to consume a supplement and are more likely to be taking vitamin D which might explain this[18,123,124]. Large global meta-analyses have also found that females had a borderline increased vitamin D status compared to males[125,126].

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Older adults

Vitamin D deficiency is prevalent in older Irish adults (>50 years) and in large studies ranged between 11 and 13 %[62,101,127]. In the largest nationally representative TILDA study (The Irish longitudinal study on ageing) of 5356 older adults, 13 % were deficient, similar to the findings of an EU meta-analysis[9,81]. In the large Trinity, Ulster, Department of Agriculture cohort study, prevalence of deficiency ranged from 13·8 and 27·3 % in older unsupplemented adults, and up to 43·6 % in those who were frail and cognitively impaired[128]. However, participants were in disease-defined cohorts, included hospital outpatients and were not representative of the wider population. As expected, deficiency was more prevalent during winter[71,72,127,129].

Regional variation in the prevalence of deficiency has been found in the nationally representative TILDA study where it was lower in Leinster compared to other provinces, likely reflecting in part variances in UVB exposure[127]. However, prevalence rates have also varied within the same areas with widely varying deficiency rates of 11–86 % in Dublin[101,130], 2–17 % in Cork[72], 10–42 % in Galway and 14–35 % in Northern Ireland[9,131]. Socioeconomic factors may play a role as suggested by the TILDA study and one large investigation in the Dublin and surrounding areas[114,132]. Urban residing older adults also had increased rates of deficiency[113], in keeping with UK findings[133], as did community dwelling older adults and nursing home residents[113] where it ranged between 35 and 42 %[114,131]. Hospital in-patients also had lower vitamin D status than those in primary care[62]. Similarly, non-community dwelling adults had lower vitamin D status in the UK[134] and in Europe at similar latitudes[135–137]. This is likely due to reduced physical activity, lack of sun exposure and poor adherence to supplementation[137,138].

In recent studies of Irish adults (>50 years), between 30 and 50 % had levels <50 nM/l, which was more prevalent in those living in northern locations and urban areas[101,114,127]. Similar findings were reported in the UK English longitudinal study of ageing and in other EU countries where it ranged from 50 to 59 %[59,81,133,139]. Seasonal decline in status was also greater with increasing age, with levels <50 nM/l in winter occurring in 64 % (aged 70–75) *v.* 34 % (aged 51–69) in 2006[72]. This was replicated by the TILDA study in 2018 which found 43 % with <50 nM/l, with higher rates in the winter in those aged 70+ *v.* 50+[127,140]. Despite a reduced capacity for dermal synthesis, UVB light and sun enjoyment were still identified as an important contributor to vitamin D status in older Irish adults[15].

Dietary and supplement intakes in adults. The most recent (2011) dietary survey in adults found that vitamin D intake in Ireland was 6·9 µg/d in older adults (>65 years), and 4·3 µg/d in those aged 18–64 years[94]. The majority (90 %) of adults aged 18–64 had intakes <10 µg/d, as did 87 % of men and 77 % of women over 65 years[94]. This indicates little improvement since the first dietary survey in 1997/1999. In fact, overall mean intake of vitamin D then was 3·4 µg/d[141,142] while 74 % of 18–64-year-olds had intakes <5 µg/d[143] and 93 % had <10 µg/d[144]. Lowest intakes were identified in younger adults (18–35 years) (mean 2·8 µg) compared to those aged 36–50 years (mean 3·4 µg) or 51–64 years (mean 5·8 µg) in 2001[141]. Recent findings are similar to those reported in the UK, Germany, Denmark, and the Netherlands though higher than that in Portugal, Spain and Italy[59]. By comparison, dietary intakes have been found to be higher in northern European countries such as Iceland, Norway, Sweden and Finland[59,145].

Meat, fish and supplements were the greatest contributors of vitamin D in the diet of Irish adults[18] similar to some EU countries such as the Netherlands. However, in countries such as France and Spain, fish and eggs are the primary and secondary sources[110,146,147]. Overall, fortified cereal/products found to contribute to 10 % of intake in the Irish diet[148], compared to 13–20 % in the UK[4].

Adolescents and adults (12–65 years) are recommended to consume 15 µg of vitamin D daily, with older adults (>65 years) who are housebound with little access to sunlight advised to take 20 µg/d[19,22]. However, only 10–17 % of Irish adults were found to be taking vitamin D supplements[18,103,140], but received more of their intake this way than from dietary sources[18,123]. In a recent (2019) TILDA report, just over 10 % of over 70s reported consuming a vitamin D supplement[140]. Supplement use was also a predictor of vitamin D status in adults[18,109,120] and older adults[15,127,128,139,140]. In fact, supplement use has been found to be the strongest determinant of vitamin D status in the Trinity, Ulster, Department of Agriculture[128] and TILDA[140] cohorts of older adults, with a mean increase of 21·4–35·4 nM/l detected[128]. Supplementation was also found to increase with age[18,143], with its contribution to dietary intake nearly twice as high in older adults aged 50+ (17 %) *v.* younger adults (9 %)[18]. This has been confirmed elsewhere[149], with higher rates in older adults (24–32 %) in the UK[57]. Supplements relating to bone health (calcium with/without vitamin D) are the most consumed in older adults[124]. Irish women are more likely to take supplements than men[15,123,124,127], where they contributed more to total vitamin D intake[143] as also found in the UK[150].

At-risk populations

Ethnic populations. The largest study to focus on an ethnic population discovered that more than two-thirds (67 %) of Southeast Asians were vitamin D deficient, but only included 186 patients who lived in the Dublin area[151]. There were only three other studies that reported vitamin D status in those of non-white ethnicity, with small sample sizes and the largest only having eighty-one adults[34,37,65]. Non-white pregnant women had greater deficiency (59–88 %) compared to Caucasians (36 %)[37], while another study identified a 19 nM/l difference in mean 25(OH)D between white and non-white pregnant women[34]. Mean 25(OH)D was also lowest in children of African ethnicity living in Ireland[65]. Ethnic minorities living in northern

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locations are known to be at increased risk of low vitamin D status due to reduced cutaneous synthesis[59,110]. By comparison, in the UK, 96 % of Southeast Asian women had levels <50 nM/l in winter and had lower serum 25(OH)D compared to white women[152]. Similarly, non-European populations, particularly pregnant women, living in Europe were at greater risk compared to their indigenous counterparts[153–156]. Despite recommendations by the European Calcified Tissue Society, there are currently no specific guidelines for higher vitamin D intake in ethnic populations in Ireland[59].

Medical conditions. Malabsorption disorders: There were five studies of adults with Crohn's disease[157–161] though sample sizes were small ($n < 100$). Prevalence of levels <50 nM/l were 50–64 %[157,158,160] in keeping with a global meta-analysis where half had levels <50 nM/l[162]. A strong seasonal effect was also found, with about 20 % having levels <50 nM/l post-summer *v.* 50 % post-winter[159,161] and with up to 90 % with levels <80 nM/l[158]. Furthermore, wintertime levels <50 nM/l were twice as common (50 %) compared to healthy controls (25 %)[159]. Crohn's patients in Ireland who had bowel surgery were also three times more likely to have levels <50 nM/l compared to non-Caucasians[163]. Comparatively in the UK, 66 % of adults with Crohn's disease had levels <50 nM/l, with significantly lower status in the winter[163]. The vast majority (88 %) of Irish patients with refractory coeliac disease had levels <50 nM/l, as did those with a recent diagnoses (58 %) compared to patients with controlled disease[164].

Other disorders. In Irish patients with multiple sclerosis, significantly greater deficiency (<25 nM/l) was found compared to age-/sex-matched controls (28·3 *v.* 19·2 %)[165]. Mean 25(OH)D levels were also higher in areas with a lower prevalence of multiple sclerosis[165]. Nearly two-thirds (65 %) of patients with systemic lupus erythematosus had levels <75 nM/l after the summer in one 2008 study[166]. In psoriasis patients, 75 % were found to have wintertime levels <50 nM/l[167] and, in individuals attending a rheumatology clinic 26 % were vitamin D deficient (<25 nM/l) and 70 % had levels <53 nM/l[168]. Deficiency prevalence was 41 % in patients with total knee arthroplasty (41 %)[169].

In adults with chronic obstructive pulmonary disease, vitamin D status was low (<50 nM/l) in 47 %, particularly in winter (75 %) and in house-bound patients[170]. In patients with obstructive sleep apnoea, 72–89 % had levels <50 nM/l, and 98 % had <75 nM/l[171,172]. This is similar to the findings of a global meta-analysis, which identified that disease severity was associated with lower vitamin D status[173]. Prevalence of levels <50 nM/l was also high in renal patients (69 %)[174] and those who had thyroidectomy (75 %)[175]. Between 35 and 50 % of Irish asthmatic children had vitamin D levels <50 nM/l[176,177], in keeping with a recent global meta-analysis[178]. Up to 40 % of children with autism had levels <50 nM/l and 75 % had <75 nM/l[176,179], consistent with a meta-analysis in 2016 that attributed lower status to factors such as increased dietary restriction and lack of time outdoors[180].

Vitamin D excess

The most recent and largest (n 100 505) cross-sectional study of adults in 2022 found a prevalence of 25(OH)D > 125 nM/l of 1·7–2·3 % though included patients mainly in the Dublin area[62]. It also identified that excess levels were higher during *v.* before the COVID pandemic (2·1 *v.* 1·7 %, $P < 0·001$) which could be due to increased dosage of new-to-market vitamin D supplements[62]. Previously, it was estimated that up to 5 % of the Irish adults in the population may be at-risk of levels >125 nM/l, with apparent increases between 1994 and 2013[104,105]. However, most studies have found a prevalence of vitamin D excess of between <1 and 3 %[18,53,101,105,113,151]. Importantly though, all of these studies are subject to significant bias as they include patients who had their vitamin D checked by request of their doctor. Higher levels of excess has been identified in Irish females (4 %) and older adults (4 %)[101] as found elsewhere[181,182]. This is likely due to females being twice as likely to use supplements, especially those over 50[123,124]. A particularly high prevalence of excess of 9 % was identified in Irish pregnant women in a randomised controlled trial though they were supplemented with up to 20 µg/d of vitamin D[38]. Vitamin D toxicity (25(OH)D level of 1617 nM/l) resulting in severe hypercalcaemia was also reported in one patient, though was explained by high-dose supplementation (250 µg/d for 2 years)[183]. Conversely, lower levels of excess (0·3–0·9 %) has been identified in nursing homes, hospital outpatient clinics, in ethnic minorities and in pregnant women[34,35,113,114,151], groups that are already at greater risk of deficiency. In the largest study of children aged over 4 (n 5524) prevalence of vitamin D excess was 0·5 % but was in higher in toddlers (4·6 %) and infants (12·1 %)[62]. A similar prevalence (0·4–0·6 %) has been found in children (>4 years) in other studies[63,66] or has not been detected at all[35].

Vitamin D status over time

There have only been two studies that have specifically examined changes in vitamin D status over time. In one that included individuals (n 43 782) in the Dublin area over 20 years (1993–2013) an average increase in 25(OH)D of 0·68 nM/l per year was estimated[184]. However, it is possible that the reason for testing may have changed over time and it did not account for potential variation in factors affecting vitamin D. More recently when comparing annual change in vitamin D status prior to *v.* during the pandemic, a 3-fold increase was noticed with a higher annual rise of 2·8 nM/l. This result however, may not be generalisable as it was based on vitamin D results from a Dublin hospital, though was attributed to a greater availability of high-dose supplements and increased public awareness[62]. While vitamin D status may have increased, particularly in some sections of the population, nearly all of the most recent studies still identify a significant of level of deficiency and levels <50 nM/l[62,101,113,140].

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Discussion

This is the first review of vitamin D status in Ireland and identifies that deficiency is commonly affecting 15–23 % of children, 13 % of adults and 15–17 % of pregnant women in the largest and most recent (<5 years) studies[34–36,62–64,66–68,127]. Deficiency was more prevalent in adolescents *v.* younger children (1–12 years), and in younger (<50 years) *v.* older adults (>50 years). There was also a particularly high prevalence in infants (<1 year) and it was also more common with increasing gestation in pregnancy. A very high rate of deficiency (67 %) was identified in Southeast Asians, though other studies of non-white ethnicity are sparse. Similarly, those with medical conditions had increased prevalence of vitamin D inadequacy, with more than half of those with respiratory conditions and the majority of those with malabsorption conditions having levels <50 nM/l.

The seasonal variation of vitamin D status was also evident with higher levels of deficiency and prevalence of levels <50 nM/l in winter. The overall prevalence of deficiency remains significant though there is some evidence to suggest a small increase in 25(OH)D levels in the past decade particularly during the COVID pandemic. The lowest vitamin D intakes were found in children (2·3 μg/d)[95] and pregnant women (1·9 μg/d)[55], with the highest (6·9 μg/d) in older adults[94]. This review indicates that low vitamin D status is widespread in the population among several groups who also have inadequate vitamin D intake.

Implications for public health

Fortification/supplementation

Guidelines for vitamin D intake in those aged 12-65 years, including at-risk groups such as pregnant women, adolescents and dark skinned ethnicities, were recently published by the FSAI and advise 15 μg/d[22]. These were based on minimising the risk of deficiency and were similar to a previously calculated 12 μg/d to avoid deficiency in most of the population[185]. However preventing winter deficiency in 97·5 % of individuals of South Asian and Black ethnicity at Irelands' latitude may require an even higher respective daily intake of 27·3 μg (1092 IU) and 33·2 μg (1328 IU). Furthermore, the guidelines do not cover a proportion of the population who have levels between 30–50 nm/l and may still be at risk of vitamin D inadequacy. For example, an intake of 25–28 μg/d may be needed to maintain wintertime sufficiency in the Irish population (>50 nM/l)[186,187] though achieving this via diet alone is not possible, so supplementation and a multi-food fortification strategy may be necessary.

Currently, fortified foods provide 11 % of total dietary vitamin D intake in adults, where they have the potential to reduce inadequacy[188]. In Irish children age 1–4 years, fortifying cow's milk and a 5 μg/d supplement in modelling studies were estimated to reduce inadequate intakes (<10 μg/d) from 95 to 12–36 %[189]. However, this would be insufficient for meeting the European Food Safety Authority (EFSA) adequate intake level (15 μg/d)[190]. Fortification of milk and bread was reported as having the potential to ensure that 70 % of older Irish adults (>50 years) meet a daily allowance of 10 μg/d[191]. In older adults, an association has been found between fortified milk and better vitamin D status[128]. Fortifying food staples such as milk and bio-enriched eggs was also estimated to reduce the wintertime decline in serum vitamin D Irish adults[192,193]. However, in a modelling study, numerous food items would need fortification to ensure vitamin D (>50 nM/l) all year around in Irish adults[194]. A more novel way using 'biofortification of foods' with vitamin D via feed modification and UV radiation in Ireland has shown potential, particularly enriched meat and could be further explored[195].

In 2003, mandatory fortification of butter/spreads and milk products in Finland enabled 91 % of the population to reach sufficiency by 2011[196], a public health measure that could be considered in Ireland. Nonetheless, some groups of the population consume less fortified foods and are less likely to benefit[197]. Exploring a multi-food system fortification approach that includes bread as well as dairy products could be considered to target a wider population[110]. Hence, care is required to ensure that excessive vitamin D consumption is avoided[198] as a small percentage of the population consuming high-dose supplements could be at risk of vitamin D toxicity[105,184]. Reassuringly, a national monitoring survey in Finland after food fortification concluded that levels above 125 nM/l were rare, though ongoing surveillance was advised[199]. Given the higher prevalence of vitamin D levels >125 nM/l recently reported in Ireland and the increased proportion of new-to-market supplements above the tolerable upper-intake level, monitoring would seem prudent[62]. Additionally, a code of practice for food business to control the level of fortification and limit its addition to designated food vehicles would be useful[200].

We acknowledge there are a number of factors that may result in a variation in vitamin D status between studies. Some were small in size, were in different geographical locations, included non-representative populations (e.g. clinical or hospital outpatient setting) and used different vitamin D assays. There is also likely to be differences in supplementation rates and other factors affecting vitamin D status between studies. While some nationally representative studies were small, the review includes several very large and recent studies.

Future research

There are limited studies of vitamin D status in non-white ethnic individuals that now comprise 5 % of the Irish population[24]. Additionally, there are no studies in minority groups such as Irish Travellers and institutionalised younger adults, all of which are groups where research is required. Furthermore, in light of low vitamin D intakes in the homeless population and nearly 9000 people in emergency accommodation in Ireland, attention could also be focused here[201,202]. Finally, meat is the primary source of dietary vitamin D in Irish adults

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though nearly one in five are vegetarian or vegan and are at-risk of deficiency, though no studies have specifically examined their vitamin D status[203].

Conclusions

Prevalence of vitamin D deficiency in Ireland was 15–17 % in pregnancy, 15–23 % in children and 13 % in adults and remains high despite some increase after the pandemic. Those at increased risk include infants (below 1 year), adolescents (12–18 years), adults (<50 years), those in the third trimester of pregnancy and non-white minorities. There is limited data in institutionalised adults, the Travelling community and those of non-European ethnicity. Given the prevalence of widespread deficiency, an updated public health policy to increase vitamin D intake, including a vitamin D awareness campaign and the careful fortification of key food groups frequently consumed by the population may be required.

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Conflict of Interest

None.

Authorship

Conceptualisation: E. L., J. B. W. and K. McC.; formal analysis: H. S.; funding acquisition: E. L., J. B. W. and K. McC.; investigation: H. S.; methodology: H. S.; project administration: H. S.; supervision: K. McC. and E. L.; writing – original draft: H. S.; writing – review and editing: H. S., E. L., M. H., J. B. W. and K. McC. All authors have read and agreed to the published version of the manuscript.

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Article

A High Prevalence of Vitamin D Deficiency Observed in an Irish South East Asian Population: A Cross-Sectional Observation Study

Eamon Laird [1,*], James Bernard Walsh [2], Susan Lanham-New [3], Maria O'Sullivan [1], Rose Anne Kenny [1], Helena Scully [2], Vivion Crowley [4] and Martin Healy [4]

1 School of Medicine, Trinity College Dublin, Dublin 2, Ireland; mosulli5@tcd.ie (M.O.); rkenny@tcd.ie (R.A.K.)
2 Mercer's Institute for Successful Ageing, St. James's Hospital, Dublin 8, Ireland; jbwalsh@tcd.ie (J.B.W.); helenascully@hotmail.com (H.S.)
3 Department of Nutritional Science, University of Surrey, Surrey GU2 7YW, UK; s.lanham-new@surrey.ac.uk
4 Department of Biochemistry, Central Pathology, St. James's Hospital, Dublin 8, Ireland; vcrowley@stjames.ie (V.C.); healymartinj@gmail.com (M.H.)
* Correspondence: lairdea@tcd.ie; Tel.: +353-1896-4342

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Abstract: At northern latitudes, non-ethnic population groups can be at an increased risk of vitamin D deficiency (defined as a 25-hydroxyvitamin D [25(OH)D] status ≤30 nmol/L). The vitamin D status of ethnic minority groups has been examined both in UK and European populations, but not in the Irish context. The aim of this study is to assess the vitamin D status from a selection of the Dublin population of South East Asian descent. A search was conducted, using the laboratory information system of St James's Hospital, Dublin, for vitamin D requests by General practitioners. From 2013 to 2016, 186 participants were identified and 25(OH)D analysis was quantified using liquid chromatography-tandem mass spectrometry (LC-MS-MS). Overall, the median age was 32 years, 51% were male, and the 25(OH)D concentration ranged from 10 to 154 nmol/L. In total, 66.7% of the total sample were vitamin D deficient and 6.7% had a 25(OH)D status greater than 50 nmol/L (the 25(OH)D concentration defined by the EU as 'sufficient'). Females had a significantly higher 25(OH)D concentration than males (25.0 vs. 18.0 nmol/L; $p = 0.001$) but both groups had a significant proportion with deficient status (56% and 76.8%, respectively). Seasonal variation of 25(OH)D was not evident while high rates of deficiency were also observed in those aged <18 years and >50 years. Given the importance of vitamin D for health, this sub-population could be at a significantly increased risk of rickets, impaired bone metabolism, and osteoporosis. In addition, vitamin D deficiency has been associated with several non-bone related conditions, including cardiovascular disease and diabetes. Currently, there is no unique vitamin D intake or vitamin D status maintenance guidelines recommended for adults of non-Irish descent; this needs to be considered by the relevant public health bodies in Ireland.

Keywords: vitamin D; population; Asian; minority; ethnic; health

1. Introduction

Vitamin D is a seco-steroid hormone with deficiency (<30 nmol/L) associated with impaired bone metabolism and increased risk of osteoporosis [1]. It has also been associated with extra-skeletal health outcomes such as cardiovascular disease (CVD), cancers, diabetes, and inflammation in many observational and prospective studies [2–4]. The main source of vitamin D is exposure to solar ultraviolet-B radiation at the correct wavelength though factors influencing this process, including latitude, seasonality, sunscreen use, ethnicity, clothing, and long periods indoors [5]. Due to the

seasonality of vitamin D synthesis at Northern latitudes, there is a heavy reliance on dietary intakes during the winter period to maintain adequate circulating concentrations [6]. Unfortunately, foods that are rich dietary sources of vitamin D are infrequently consumed and many food products are not fortified with vitamin D [6]. Thus, significant rates of vitamin D deficiency and insufficiency have been reported in countries such as Ireland, the UK, and several other European states [7]. For instance, recent data from the Irish Longitudinal Study on Aging (TILDA) reported one in eight older Caucasian Irish adults were vitamin D deficient, which increased to one in four during the winter period [8].

Recent studies have shown that the vitamin D status of immigrant populations is significantly poorer when compared to the indigenous population of countries investigated [9]. This is particularly true of the migrant Asian population where a large number of investigations in the UK have demonstrated a high prevalence of hypovitaminosis D exists in this group [10–13]. For instance, in 6433 South Asians from the UK Biobank, 92% had blood vitamin D levels <50 nmol/L [14]. To date, however, there has been no estimation of vitamin D status in the Asian migrant population in Ireland, a group comprising approximately 79,000 (1.7%) of the total population [15].

The aims of this cross-sectional observational study, therefore, are to assess the vitamin D status for a selection of the Dublin (53.3° N; capital city) population of South East Asian descent and to provide pilot data for this population. This may allow a future intervention strategy to be considered.

2. Materials and Methods

2.1. Study Design

A search was conducted using the Biochemistry Department laboratory information system (iSOFT Telepath®) of St James's Hospital, Dublin, Ireland (53.3° N) for vitamin D requests by general practitioners (GPs) known to take patients self-identified as Asian (non-Chinese). From 2013 to 2016, 186 participants were found. After identification, all participants were given an anonymized code and recognition materials were removed from the analysis database. The exclusion criteria included those who were non-Asian, aged <2 years, missing demographic data (such as age or sex), or were residing in nursing home locations. Seasons were defined as Winter: (December–February), Spring: (March–May), Summer: (June–August), and Autumn: (September–November). Duplications within a specified season were averaged, with the duplicate being excluded. Seasons were collated and, given the latitude of Ireland, grouped in either low vitamin D synthesis period (October to March) or high vitamin D synthesis period (April to September). The joint research ethics committee at St James's Hospital/Tallaght University Hospital (SJH/TUH) granted ethical approval for this study (Ref: 5475), which was conducted according to the guidelines laid down in the Declaration of Helsinki 1964.

2.2. Laboratory Analysis

Samples for vitamin D analysis included total 25-hydroxy-vitamin D (25(OH)D) (D2 and D3) concentrations, which were quantified by a validated method (Chromsystems Instruments and Chemicals GmbH; MassChrom 25-OH-Vitamin D3/D2) using liquid chromatography-tandem mass spectrometry (LC-MS-MS) (API 4000; AB SCIEX, Framingham, MA, USA) and analyzed in the Biochemistry Department of St James's Hospital (accredited to ISO 15189). The quality and accuracy of the method was monitored by the use of internal quality controls, participation in the Vitamin D External Quality Assessment Scheme (DEQAS), and the use of the National Institute of Standards and Technology (NIST) 972 vitamin D standard reference material. The respective inter- and intra-assay coefficients of variation were 5.7% and 4.5%. For this study, vitamin D 'sufficiency' was defined as a serum 25(OH)D concentration ≥50 nmol/L, vitamin D 'insufficiency' as 30 to 49.9 nmol/L, and risk of vitamin D deficiency as <30 nmol/L [1]. High vitamin D status was defined as >125 nmol/L [1]. Intact parathyroid hormone (PTH) was measured at St. James's Hospital, Dublin using an electrochemiluminescence immunoassay (ECLIA) (Modular E170, Roche Diagnostics, Burgess Hill, UK) with an inter-assay CV of <2.9% and an assay measurement range of 1.2 to 5000 pg/mL. Calcium was assayed on a Roche c701

chemistry analyzer (Roche Diagnostics, Burgess Hill, UK) using a proprietary calcium kit (Calcium Gen 2). The assay measurement range was 0.20 to 7.5 nmol/L with an interassay precision of <2.6%.

2.3. Statistical Analysis

Statistical analyses were carried out using the SPSS, version 24.0 (IBM Corp., Armonk, NY, USA, 2019). Data were checked for normality by the Kolmogorov-Smirnov test and Q-Q plots and, where appropriate, data were log-transformed. Data within the tables are expressed as geometric-means with standard deviation (SD). Where appropriate, an independent Student's *t*-test, one-way ANOVA, or, for categorical variables, chi-square analysis or Fisher's (where *n* was <5) were applied to determine statistical significance. Statistical significance was accepted at a *p* value of <0.05).

3. Results

The population characteristics are displayed in Table 1 (*n* 186). Overall, the median age was 32 years, 51% were male, and <5% were aged <18 or >50 years. There was no significant difference in the mean age between genders, though females had a slightly higher proportion aged 18 to 50 years ($p = 0.047$). The sample contained significantly less females than males from the winter period (19.8% vs. 44.2%; $p = 0.001$) and a slightly higher proportion of females during autumn (37.3% vs. 21.1%; $p = 0.011$). However, females had a significantly higher PTH ($p = 0.044$) and lower calcium ($p = 0.004$) concentration in comparison to males. The total sample 25(OH)D concentration ranged from 10 to 154 nmol/L with females having a higher median 25(OH)D compared to males (25.0 vs. 18.0 nmol/L; $p = 0.004$) but both groups still fell below the risk of deficiency cut-point of 30 nmol/L. The average 25(OH)D concentration for those aged <18 years was 20.0 nmol/L (14.0 to 37.0 nmol/L) while for those aged >50 years it was 26.0 nmol/L (14.5 to 50.5 nmol/L). Only one participant (0.5% of the sample) had a 25(OH)D concentration >125 nmol/L.

Table 1. Population characteristics of the South East Asian participants [1].

	Male	**Female**	***p*-Value**
	n 95	*n* 91	
Age (years)	31.0 (27.0, 36.0)	33.0 (26.0, 38.0)	0.178
<18 *n* (%)	2 (2.1)	4 (4.4)	0.437
18 to 50 *n* (%)	90 (94.7)	78 (85.7)	0.047
>50 *n* (%)	3 (3.2)	9 (9.9)	0.077
Season sampled *n* (%)			
Winter	42 (44.2)	18 (19.8)	0.001
Spring	17 (17.9)	16 (17.6)	0.956
Summer	16 (16.8)	23 (25.3)	0.207
Autumn	20 (21.1)	34 (37.3)	0.016
Bone biochemistry			
25(OH)D (nmol/L)	18.0 (27.0, 36.0)	25.0 (17.0, 30.0)	0.004
PTH (pg/mL)	41.6 (31.7, 53.8)	43.8 (35.1, 71.0)	0.044
Calcium (mmol/L)	2.35 (2.29, 2.41)	2.26 (2.22, 2.35)	<0.001

[1] Values are displayed as *n* (%) or medians (25 to 75th percentile). Differences between genders for continuous variables were assessed using an independent *t*-Test while differences in categorical variables were assessed using chi-square analysis or Fisher's where *n* was <5. Normal reference range for parathyroid hormone (PTH): 15 to 65 pg/mL; Normal reference range for calcium: 2.15 to 2.50 mmol/L.

In total, 66.7% of the total sample were vitamin D deficient; males and younger adults (<18 years) had higher deficiency rates in comparison to females and older adults (>50 years). When the seasons were grouped into the 'low' and 'high' vitamin D synthesis periods, there was no significant difference in 25(OH)D concentration between the two periods (20.0 vs. 23.0 nmol/L, respectively; $p = 0.223$). Males had a higher percentage of deficiency compared to females in the low synthesis period (79.3 vs.

51.5%; $p = 0.009$) and a lower percentage with sufficient status (5.2 vs. 27.3%; $p = 0.004$) (Figure 1). There was no gender difference when examined by the high synthesis period (Figure 2). All age groups had ≥50% risk of 25(OH)D deficiency regardless of the synthesis period sampled (Figures 3 and 4).

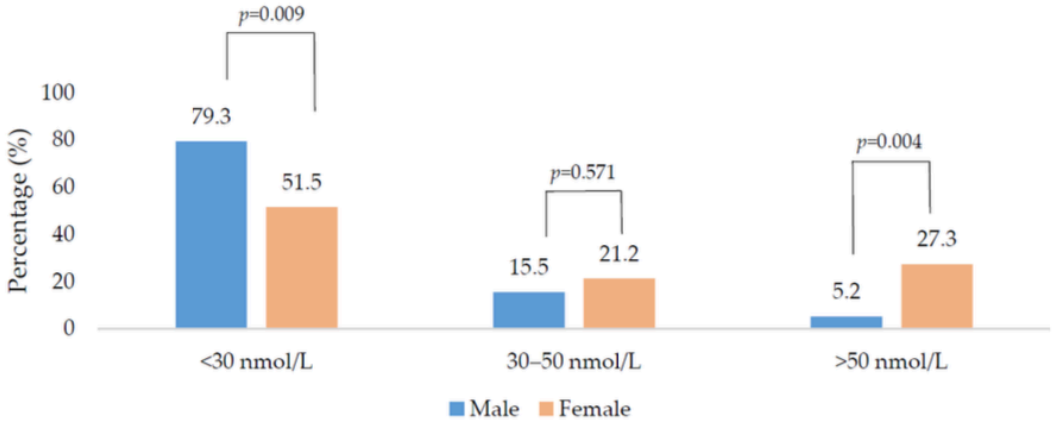

Figure 1. Vitamin D status of the population during the low vitamin D synthesis period (October to March) sub-divided by gender. *p*-values were derived from chi-square analysis.

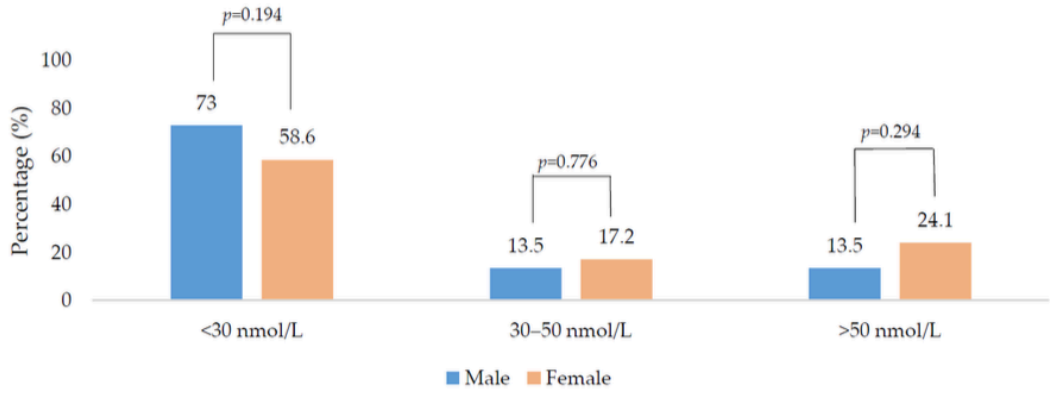

Figure 2. Vitamin D status of the population during the high vitamin D synthesis period (April to September) sub-divided by gender. *p*-values were derived from chi-square analysis.

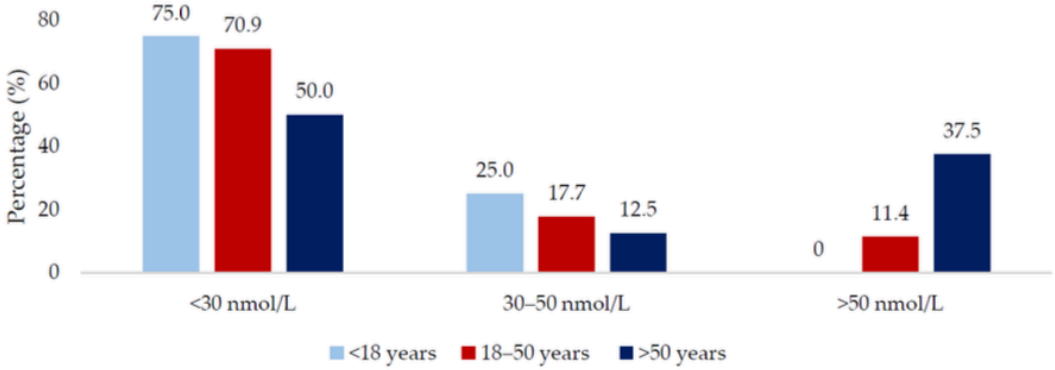

Figure 3. Vitamin D status of the population during the low vitamin D synthesis period (October to March) sub-divided by age group.

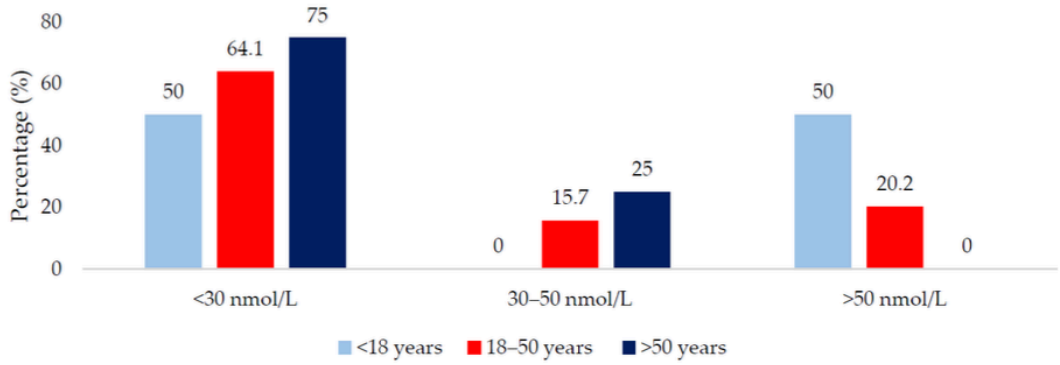

Figure 4. Vitamin D status of the population during the high vitamin D synthesis period (April to September) sub-divided by age group.

In relation to biochemical markers of bone health (Table 2), concentrations of PTH were significantly higher in participants who were 25(OH)D deficient compared to sufficient (45.5 vs. 36.1 pg/mL).

Table 2. Bone marker concentrations of the participants by 25(OH)D status [1].

	<30 nmol/L (Deficient)	30–50 nmol/L (Insufficient)	>50 nmol/L (Sufficient)
Total			
PTH (pg/mL)	45.5 (36.5, 65.1) [a]	41.8 (28.1, 50.0) [a,b]	36.1 (25.4, 43.8) [b]
Calcium (mmol/L)	2.33 (2.25, 2.39)	2.32 (2.25, 2.38)	2.26 (2.24, 2.35)
Men			
PTH (pg/mL)	45.5 (33.1, 58.1) [a]	37.1 (28.9, 46.1) [a]	20.4 (16.6, 39.2) [b]
Calcium (mmol/L)	2.35 (2.31, 2.41)	2.35 (2.30, 2.43)	2.26 (2.21, 2.37)
Women			
PTH (pg/mL)	45.8 (38.9, 89.0)	46.3 (25.6, 55.7)	39.3 (33.2, 48.1)
Calcium (mmol/L)	2.25 (2.20, 2.35)	2.26 (2.19, 2.37)	2.27 (2.24, 2.35)

[1] Values are displayed as medians (25 to 7th percentile). Differences were assessed by One Way ANOVA with Bonferroni correction. Values in the same row with different superscript letters are significantly different, $p < 0.05$. Normal reference range for PTH: 15 to 65 pg/mL; Normal reference range for calcium: 2.15 to 2.50 mmol/L.

4. Discussion

To our knowledge, this is the first study in Ireland to examine the vitamin D status of Irish South East Asians. Our findings reflect previous studies demonstrating poor vitamin D status among non-western immigrants living in European countries. In this cohort, over 66% were vitamin D deficient, which was more than five times the estimated deficiency rate for Caucasian Irish adults (13%). These high rates of deficiency were observed regardless of vitamin D synthesis period, gender, or age. In addition, participants with vitamin D deficiency had a significantly higher PTH concentration compared to those who were sufficient. Raised PTH reflects low or insufficient vitamin D status and the combination of both of these can be associated with high bone turnover, which may result in net bone resorption [1]. Extended periods of vitamin D deficiency have been associated with muscle weakness, bone demineralization resulting in rickets or osteomalacia, pain, fractures, and frailty.

This population group could also be at risk of other non-skeletal chronic diseases that are thought to be associated with vitamin D deficiency including type 2 diabetes and heart disease [2,3]. Several reports have shown that South East Asian populations have an increased incidence prevalence of these conditions [16,17]. In the current context of COVID-19, research evidence [18] has shown that this group may also have poorer outcomes with some suggesting a possible mechanistic link with low vitamin D status given its role in supporting the immune system [4,19].

Our findings of high deficiency rates are similar to observations from the UK and Europe [9–14]. High rates of deficiency have been reported in South Asians arriving in Norway (75% deficient) [20] along with low 25(OH)D concentrations in Asian children residing in London [21] and an increased risk of osteomalacia in adult Asian groups also living in the UK [22]. These high deficiency rates are not just limited to the Asian ethnic group but appear to be common among most immigrant groups that travel from the lower latitudes to the Northern latitude countries [23–25]. A number of reasons for the high deficiency rates can be speculated. South East Asians typically have higher concentrations of skin melatonin resulting in a longer time period required to synthesize vitamin D at higher latitude countries such as Ireland [26]. This could further be compounded by the fact that in Ireland meaningful vitamin D synthesis can only occur from late March to early September while the temperate cloudy climate can further reduce synthesis [27]. Furthermore, the South East Asian population has a rich cultural history where reduced skin exposure to UV light may result in a further reduction of vitamin D synthesis [28]. However, in our study, men typically had higher levels of deficiency than women—this is a common observation that is being reported across many vitamin D studies. There is no firm hypothesis to account for this difference—it is possible the different fat mass and muscle composition may have an effect while differences in the metabolic utilization or tissue priority for vitamin D could be different in the sexes.

In terms of dietary intakes of vitamin D, scant information exists of the vitamin D dietary intakes of Irish Asians. The traditional South East Asian diet has been reported to be low in foods containing vitamin D [29]. Mandatory fortification of foods with vitamin D does not occur in Ireland and it is subject only to a voluntary 'custom' with few foods containing vitamin D apart from some milk and yoghurt products. Other dietary lifestyle factors may influence vitamin D including specific cultural practices such as Betel nut chewing which is common among Asian populations. This aggravates vitamin D deficiency by increasing 25-hydroxylase activity and decreasing 1,25-di-hydroxyvitamin D systemic concentrations [30]. There is no epidemiological information regarding Betel nut chewing among the Irish Asian population.

Recently, the Food Safety Authority of Ireland (FSAI) updated the national vitamin D intake guidelines for the Irish population as a whole. [31]. In the policy document, it was recommended that food (including supplements) needs to provide 10 µg of vitamin D every day for everyone aged ≥5 years. Few foods, however, contain the necessary vitamin D concentrations and those that do are infrequently consumed. This may be due to lack of availability or costs of the food products. There may also be cultural traditions regarding different food types including, in particular, vegan diets. Importantly in the current context, although other international policy documents address the vitamin D needs of specific population sub-sets, the FSAI does not do so. However, across the EU there is little harmonization of vitamin D supplementation and fortification policies and mandatory food fortification with vitamin D is rarely implemented. Furthermore, policy documents can include confusing and contradictory information, which makes it difficult to translate guidelines to specific settings [32]. In the UK, both the Scientific Advisory Committee on Nutrition (SACN) and the National Institute for Health and Care Excellence (NICE) have made recommendations for 'at risk' groups regarding supplementation with vitamin D [33,34]. These risk groups include those on vegetarian diets, those who have dark skin pigmentation, those who have limited exposure to UVB light because of cultural or lifestyle practices, and would include those in the Asian community. A 'multi-agency' approach is recommended to improve communication and education relating to vitamin D intake and to encourage behavioral involvement in the uptake of recommendations.

This study gives an overview of the vitamin D status of a sub-set of the Irish Asian population and is the first report to do so. It reviews both males and females across the age spectrum. Vitamin D analysis was assessed using LC-MS/MS which is the gold standard for vitamin D assessment. Limitations include the small sample size with no information on dietary vitamin D intakes, sun exposure, other demographics, or medication/supplement use as this information was not collected on the GP electronic sample system. The study was performed, however, to illustrate low vitamin D levels in

this ethnic group with a view to designing follow-up studies and formulating an approach to assist in correcting the vitamin D deficit.

5. Conclusions

In conclusion, we observed high levels of vitamin D deficiency in a sample of South East Asian Irish. Their 25(OH)D concentration remained low throughout the year and was unaffected by seasonality. Vitamin D is universally accepted to have a critical role in normal bone metabolism. In addition, many studies have associated low vitamin D status with numerous chronic and systemic conditions. This population group is known to be at a higher risk for cardiovascular disease/diabetes and an association with chronically low vitamin D levels has been speculated. Its role in a normally functioning immune system has also been brought to the fore with the onset of COVID-19. It is critically important that the Government agencies tasked with developing policies for vitamin D requirements address sub-groups such as those described here who are at particular risk for deficiency.

Author Contributions: M.H. and E.L. conceived and designed the study; S.L.-N., R.A.K., M.O., J.B.W., H.S. and V.C. provided data interpretation; all authors approved the manuscript. All authors have read and agreed to the published version of the manuscript.

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Chapter 3: Geomapping Vitamin D Status in a Large City and Surrounding Population - Exploring the Impact of Location and Demographics

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Geomapping Vitamin D Status in a Large City and Surrounding Population—Exploring the Impact of Location and Demographics

Helena Scully [1,*], Eamon Laird [2], Martin Healy [3], James Bernard Walsh [1], Vivion Crowley [3] and Kevin McCarroll [1]

[1] Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin 8, Ireland; jbwalsh@tcd.ie (J.B.W.); kmccarroll@stjames.ie (K.M.C.)
[2] School of Medicine, Trinity College Dublin, Dublin 2, Ireland; Lairdea@tcd.ie
[3] Department of Biochemistry, St. James's Hospital, Dublin 8, Ireland; mhealy@stjames.ie (M.H.); vcrowley@stjames.ie (V.C.)
* Correspondence: hscully@stjames.ie

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Abstract: Vitamin D status was assessed in a large urban area to compare differences in deficiency and to geomap the results. In total, 36,466 participants from 28 geographical areas were identified in this cross-sectional, retrospective analysis of general practitioner (GP)-requested 25(OH)D tests at St James's Hospital, Dublin between 2014 and 2018. The population were community-dwelling adults, median age 50.7 (18–109 years) with 15% of participants deficient (<30 nmol/L), rising to 23% in the winter. Deficiency was greatest in younger (18–39 years) and oldest (80+ years) adults, and in males versus females (18% vs. 11%, $p < 0.001$). Season was the biggest predictor of deficiency (OR 4.44, winter versus summer, $p < 0.001$), followed by location (west Dublin OR 2.17, north Dublin 1.54, south Dublin 1.42 versus rest of Ireland, $p < 0.001$) where several urban areas with an increased prevalence of deficiency were identified. There was no improvement in 25(OH)D over the 5-year period despite increased levels of testing. One in four adults were vitamin D deficient in the winter, with significant variations across locations and demographics. Overall this study identifies key groups at risk of 25(OH)D deficiency and insufficiency, thus providing important public health information for the targeting of interventions to optimise 25(OH)D. Mandatory fortification may be necessary to address this widespread inadequacy.

Keywords: vitamin D; 25(OH)D; vitamin D deficiency; geomapping; Ireland; Europe

1. Introduction

Vitamin D has become the focus of increased interest globally, with the number of web searches rising year on year, peaking in the winter and now eclipsing that of Vitamin C [1]. Vitamin D has an established role in maintaining normal bone health, being required for the adequate absorption of calcium and phosphate from the gut and thereby mineralisation of the skeleton. Deficiency causes rickets in children and osteomalacia in adults and it can also exacerbate or contribute to the development of osteoporosis. Furthermore, vitamin D deficiency can lead to muscle weakness and may increase the risk of falls and fractures [2]. More recently, research has demonstrated associations with chronic conditions such as diabetes [3], inflammation [4], cardiovascular disease [5], depression [6] and cancer [7].

Vitamin D is unique as it is the only vitamin that can be synthesised endogenously via the action of ultraviolet-B (UVB) light on the skin. In fact, the majority (90%) of our vitamin D is derived

in this way, making it a highly variable source. Geographical latitude, time of year, cloud cover, sunscreen use, skin pigment, obesity, religious dress and age can all affect UVB vitamin D synthesis [2,8]. In locations greater than 30° north or south latitude, a 'vitamin D winter' exists between October and March when little or no vitamin D can be produced due to limited UVB penetration [9]. During this period, we rely on vitamin D through diet alone though in countries such as Ireland, where there is no mandatory vitamin D fortification of foods, it is difficult to reach the recommended daily intake (10 μg/day) as sources in the diet (such as oily fish) are limited or are often not consumed [10]. As a result, a significant proportion of the population is at risk of deficiency (25-hydroxyvitamin D {25(OH)D < 30 nmol/L}) [11]. In particular, those most at risk include indoor or night-shift workers [12], housebound or noncommunity dwellers [13] or the elderly with reduced capacity for cutaneous synthesis [14].

It is difficult to compare studies of vitamin D status as they involve different populations and thresholds for defining deficiency. In Ireland, the National Adult Nutrition Survey (n = 1132) found that 21% of 18–84-year-olds were deficient (<30 nmol/L), although this included a small number of older adults [10]. The only other nationally representative Irish study was The Irish Longitudinal Study on Ageing (TILDA) (n = 5356), which found that 13.1% were deficient (<30 nmol/L), rising to 23% in the winter [14]. One study of Irish rural and urban dwellers (n = 17,590) identified that 15.9% of adults were deficient (<25 nmol/L) but included only those in the west of the country [15]. The Trinity Ulster Department of Agriculture (TUDA) Study of older Irish adults (>60 years, n = 4444) reported that between 13.8% to 43.6% were deficient (<30 nmol/L), though had participants from disease defined cohorts [16]. However, it is not only older adults who are at risk. For example, in a study of adolescents across 9 EU countries, 15% were deficient (<27.5 nmol/L) and 27% insufficient (27.5–49.9 nmol/L) [17].

Environment is an important determinant of health and when combined with other data can be used to create geomaps. To date, few studies have applied this technique when exploring vitamin D status. Of note, geomapping of a large urban area in Calgary, Canada identified population clusters where education and immigration status were the strongest predictors of 25(OH)D [18]. Moreover, vitamin D status has also been geomapped in a population of free-living adults in Dublin, Ireland (53 N°). This study found that 15.2% were deficient (<30 nmol/L) in winter, improving to 10.8% in the summer, but with significant variation by postal code area [19]. However, the vitamin D measurement was limited to a one-year period.

The current study aims to investigate the vitamin D status of community-dwelling Irish adults over a 5-year time period (across a broad age range) living in Dublin and surrounding areas who had their vitamin D tested in primary care by request of their general practitioner (GP). A key objective is to explore the effects of gender, age, season and geographical area on vitamin D status. Finally, in what is the largest study of its type in Europe, we aim to create a geomap that visually depicts the prevalence of vitamin D deficiency by location.

2. Materials and Methods

2.1. Data Collection

St James's hospital (SJH) is the largest academic teaching hospital in the Republic of Ireland serving a population of approximately 350,000 people. It is located in Dublin city, on the east coast of Ireland (53.35° North latitude) and receives the majority of referrals from Dublin city and the greater Dublin area. A search was completed for vitamin D requests from primary care GPs at the SJH biochemistry department via its information system (iSOFT Telepath®). Samples requested between 2014 and 2018 (inclusively) were selected for a retrospective cross-sectional analysis. The exclusion criteria were: aged <18 years, missing or incomplete demographic data, noncommunity dwelling address (e.g., nursing home or hospital) or address outside of the Republic of Ireland. Repeat vitamin D results were excluded to avoid pseudo-replication.

Dublin area postal codes were used to record participants residence. Dublin areas are represented by postal codes (D1 to D24) with odd numbers for locations in north Dublin and even

numbers in south Dublin. Some locations have no postal code but a specific name or are known only as being in north or south. County Dublin was also categorised into three main areas: North Dublin (D1, D3, D5, D7, D9, D11, D13/17, North County Dublin); south Dublin (D2, D4, D6/6W, D8, D10, D12, D14/16, D18, south County Dublin); west Dublin (D15, D20, D22, D24, Lucan). County Kildare was split into north (including the towns of Leixlip, Maynooth, Celbridge and Kilcock) and rest of Kildare. Residents in Counties Meath and Wicklow were also designated separately. Participants living in the province of Leinster (but not in Dublin or adjacent counties of Meath, Kildare and Wicklow) were classified as 'rest of Leinster'. Those residing outside of the above locations were categorised as 'rest of Ireland'.

2.2. Ethics

The joint research ethics committee at St James's Hospital/Tallaght University Hospital (SJH/TUH) granted ethical approval for this study (Ref: 5475) which was conducted according to the guidelines laid down in the Declaration of Helsinki 1964.

2.3. Serum 25(OH)D Measurement

The nutritional marker of vitamin D status, serum concentration of 25(OH)D (total 25(OH)D2 and 25(OH)D3), was quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (API 4000; AB SCIEX) using a fully validated method (Chromsystems Instruments and Chemicals GmbH, Gräfelfing, Germany MassChrom 25-OH-Vitamin D3/D2) at the Biochemistry Department of SJH, which is fully accredited to ISO 15189:2012 standard. Quality is monitored by assay of internal quality controls, participation in the Vitamin D External Quality Assessment Scheme (DEQAS) and the utilisation of the National Institute of Standards and Technology (NIST) 972 25(OH)D standard reference material (SRM 972) to determine accuracy. The limit of quantification was 9 nmol/L, with values below this assigned as 9 nmol/L. The respective inter-and intra- assay coefficients of variation are 5.7% and 4.5%.

There is a lack of agreement as to what constitutes vitamin D deficiency or suboptimal vitamin D status [20,21]. The Institute of Medicine (IOM) defines risk of deficiency at as <30 nmol, 30–49.9 nmol/L as being at risk of inadequacy and replete status at ≥50 nmol/L [11] while others define deficiency as <25 nmol/L [2]. A 25(OH)D level >125 nmol/L may be harmful to health [11,22]. In this study, we defined deficiency as <30 nmol/L, insufficiency as 30.0–49.9 nmol/L and sufficiency as ≥50 nmol/L, as used elsewhere [11,19]. Participants with 25(OH)D level >125 nmol/L were also identified. Seasons were defined as winter (December, January, February), Spring (March, April, May), Summer (June, July, August) and Autumn (September, October, November).

2.4. Statistics

Statistical analysis was carried out using SPSS (Version 24, IBM Corp., Armonk, NY, USA.) Data were checked for normality by the Kilmogorov-Smirnov test and Q-Q plot and transformed where necessary. Data reported in tables and maps are expressed as geometric mean with standard deviation (SD). Independent sample t-tests, one-way ANOVA for continuous and Chi-square for categorical variables were performed as appropriate to assess statistical significance ($p < 0.05$). Postal districts with smaller populations ($n < 100$) but adjacent to each other and with similar demographics were combined for the analysis (D6/D6W, D13/17 and D14/16). Multinomial regression was used to explore the determinants of 25(OH)D status including age, gender, season of sampling and geographical area. The areas of 'rest of Leinster' and 'rest of Ireland' were combined to form 'outside Dublin' as the reference area.

2.5. Geomapping of Participants

A colour-coded map was created depicting the prevalence of deficiency for the areas sampled in the seasons of summer and winter, with categorisation based on the prevalence rates of

25(OH)D<30 nmol/L as follows: <10%, 11–20%, 21–29% and >30%. Areas with smaller numbers (n < 120) that were likely to be nonrepresentative were excluded from our map.

An ANOVA analysis was used to identify mean differences in 25(OH)D between areas in the winter and summer (see Appendix A), and cluster maps were created. These depict differences between 25(OH)D across several areas, categorised with equal distribution based on median values for winter (<10 nmol/L, 10–20 nmol/L, >20 nmol/L) and summer (<10 nmol/L, >10 nmol/L).

3. Results

3.1. Demographics

There were 51,651 serum 25(OH)D results reported to primary care GPs between 2014 and 2018, of which 36,466 (70.6%) met the inclusion criteria (Figure 1). The population and area demographics are shown in the respective Table 1 and Table 2. There was a relatively even distribution of samples across all seasons. The median age was 50.7 years, ranging from 18 to 109 years. We sampled 28 areas, with requests from County Dublin and Kildare comprising the majority (97%). Approximately 15 areas had 25(OH)D results for at least 500 people, Dublin 13/17 being the smallest (n = 107) and north Kildare the largest (n = 5734). Those in Dublin 1 were the youngest (35.9 ± 11.6 years) with 88% aged under 50 years, while those in Dublin 20 were the oldest (57.8 ± 17.5 years). The majority of requests (72%) were for females. This varied by location, ranging from 64% in Dublin 20 to 80% in Dublin 3.

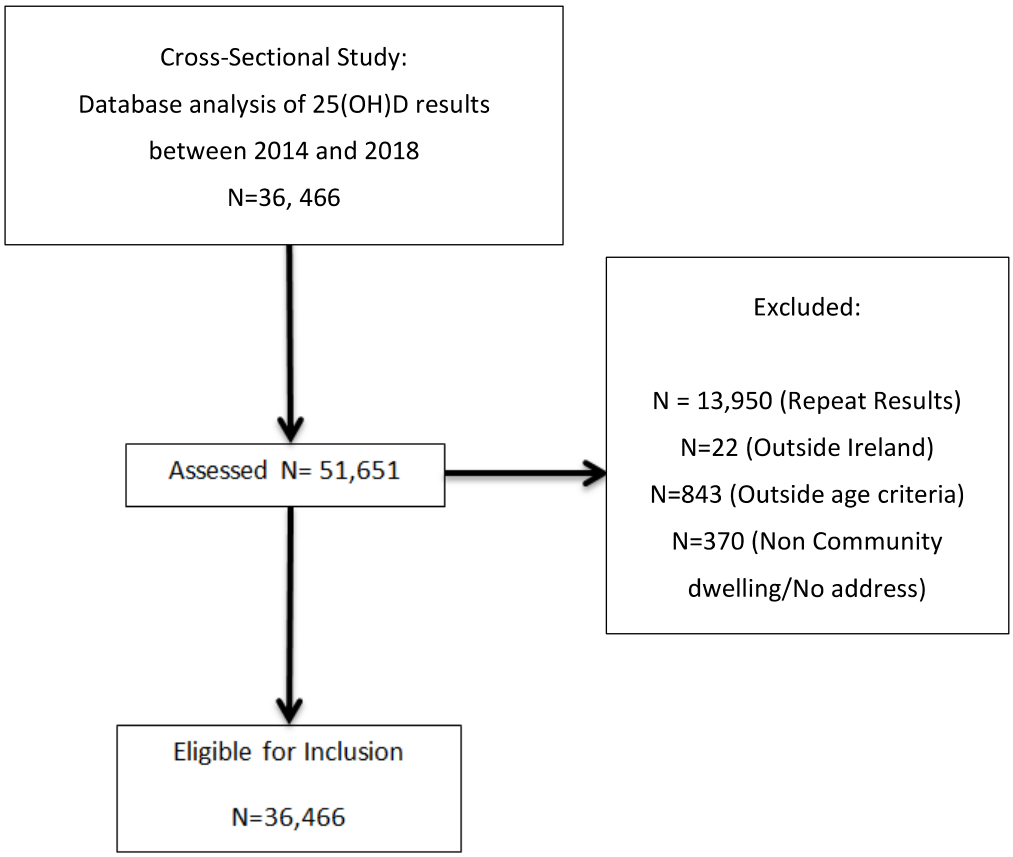

Figure 1. Recruitment Flow Diagram.

Table 1. Demographics.

Demographics		N	%	GM Mean (SD)
Age Category (years)	18–39	11,319	31	47.8 (30.8)
	40–49	6977	19	50.3 (28.5)
	50–59	6328	17	56.5 (29.9)
	60–69	5753	16	62.1 (30.0)
	70–79	3865	11	61.7 (31.8)
	80–89	2003	5	58.1 (33.0)
	>90	221	1	54.1 (33.7)
Age groups (years)	<50	18,941	52	48.8 (29.8)
	>50	17,525	48	59.7 (30.8)
Area	North Dublin	1758	5	50.8 (30.9)
	South Dublin	18,827	52	54.5 (31.7)
	West Dublin	8310	23	50.6 (30.3)
	Outside Dublin	7571	21	55.8 (29.5)
Season	Winter	8101	22	46.8 (30.3)
	Spring	10,321	28	48.9 (30.4)
	Summer	9353	26	58.6 (30.5)
	Autumn	8691	24	63.0 (29.4)
Gender	Male	10,335	28	49.7 (29.0)
	Female	261	72	55.1 (31.3)
Total		36,466		53.8 (30.78)

Table 2. Area Demographics.

Area	N	GM Mean (SD)	<50 Years (%)	Female (%)
Dublin 1	290	45.5 (31.4)	88	73
Dublin 2	639	49.5 (29.6)	74	72
Dublin 3	219	54.9 (33.5)	78	80
Dublin 4	662	58.8 (33.0)	57	74
Dublin 5	111	54.6 (30.7)	75	77
Dublin 6/6W	5273	58.6 (31.1)	44	76
Dublin 7	496	51.4 (31.5)	80	74
Dublin 8	2915	49.1 (31.9)	61	74
Dublin 9	173	51.0 (29.5)	77	79
Dublin 10	846	50.8 (30.5)	42	72
Dublin 11	142	46.2 (27.3)	86	75
Dublin 12	3375	54.1 (31.8)	36	76
Dublin 13/17	107	52.0 (35.9)	82	78
Dublin 14/16	4129	59.9 (30.8)	36	70
Dublin 15	480	50.3 (31.5)	75	70
Dublin 18	372	54.0 (36.9)	72	66
Dublin 20	1353	54.3 (29.8)	34	64
Dublin 22	719	49.8 (29.5)	61	68
Dublin 24	750	52.3 (30.1)	58	73
North Co. Dublin	220	50.7 (27.7)	77	79
South Co. Dublin	616	55.9 (29.7)	58	72
Lucan, Co. Dublin	5008	46.5 (30.8)	64	69
North Co. Kildare	5734	56.1 (27.5)	49	68
Rest of Kildare	757	56.5 (29.0)	52	69
Co. Meath	502	56.2 (31.3)	66	75
Co. Wicklow	164	58.2 (28.8)	58	71
Rest of Leinster	209	54.1 (29.9)	67	72
Rest of Ireland	205	53.8 (30.5)	78	70
Total	36,466	53.8 (30.8)	52	72

Note: County abbreviated as Co.

The 25(OH)D geometric mean was lowest in winter (46.8 ± 30.3 nmol/L) and highest in autumn (63.0 ± 29.4 nmol/L) versus spring (48.9 ± 30.4 nmol/L) or summer (58.6 ± 30.5 nmol/L). Females had higher 25(OH)D versus males (55.1 ± 31.3 nmol/L vs. 49.7 ± 29.0 nmol/L, $p < 0.001$).

3.2. 25(OH)D Status by Year, Age and Gender

The 25(OH)D status over the five-year period is shown in Table 3, with the proportion in each category (deficient, insufficient and >125 nmol/L) split by age and gender. Overall, there was a 58% increase in vitamin D testing from 2014 to 2018. The proportion who were deficient, insufficient and who had 25(OH)D >125 nmol/L was relatively stable over time at 15%, 23% and 3% respectively. When dichotomised by age, we found that those <50 years had a higher level of deficiency versus those ≥50 years (18% vs. 11%, $p < 0.001$).

Table 3. 25(OH)D categorised by year, age and gender.

Year	N	Total (%)			Age						*p*-Value	Gender						*p*-Value
					<50 Years (%)			>50 Years (%)				Female (%)			Male (%)			
		<30	30–49	>125	<30	30–49	>125	<30	30–49	>125		<30	30–49	>125	<30	30–49	>125	
2014	5394	13	21	3	18	25	3	9	18	4	<0.001	12	20	3	16	25	2	<0.001
2015	6010	17	24	2	22	29	2	12	20	3	<0.001	16	23	3	19	29	1	<0.001
2016	7625	16	23	3	20	26	2	11	20	4	<0.001	15	21	4	18	27	2	<0.001
2017	8869	14	23	3	16	26	2	11	18	4	<0.001	12	22	3	17	25	2	<0.001
2018	8568	15	24	3	17	27	3	12	20	4	<0.001	14	23	4	17	28	2	<0.001
Total	36,466	15	23	3	18	27	2	11	19	4		14	22	3	17	27	2	

Those aged ≥50 years were more likely to have a 25(OH)D > 125 nmol/L (4% vs. 2%, $p < 0.001$) as were females (3% vs. 2%, $p < 0.001$) and those sampled in the summer ($p < 0.001$). Overall, the prevalence of deficiency was greater in males versus females (17% vs. 14%, $p < 0.001$) as was insufficiency (27% vs. 22%, $p < 0.001$).

Figure 2 illustrates 25(OH)D status in various age categories. Those who were youngest (18–39 years) had the highest prevalence of deficiency (21%) and insufficiency (26%). This prevalence was only matched by those in the very oldest age group (>90+ years). In fact, there was a 'U' shaped relationship, with the best vitamin D status in those aged 60–69, and then progressively declining when moving towards both the younger and older ends of the age spectrum.

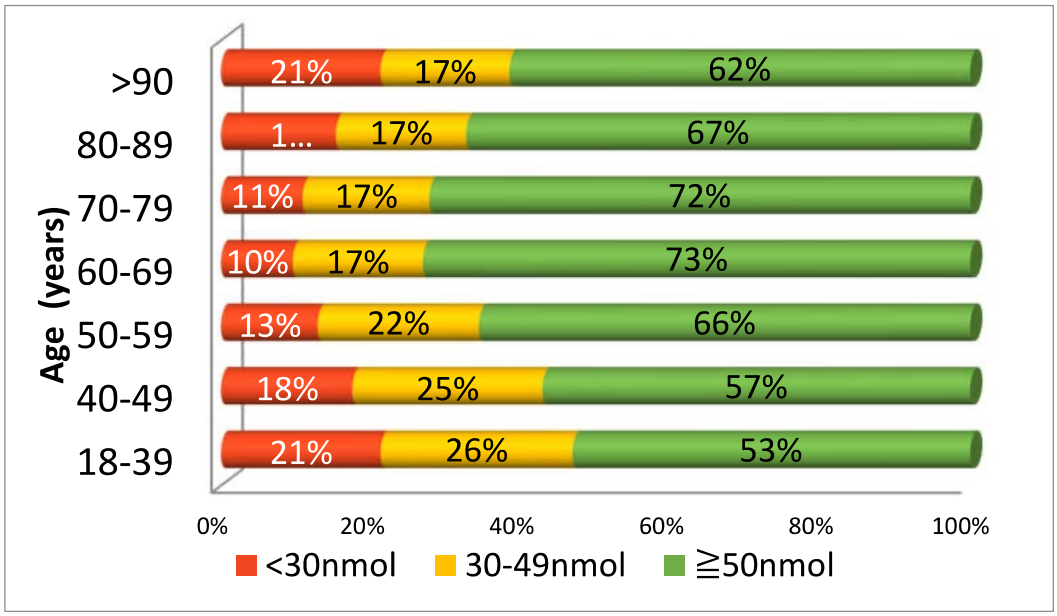

Figure 2. 25(OH)D status in different age categories.

3.3. (OH)D Status by Area—Effect of Season

The prevalence of deficiency and insufficiency is shown for each area and categorised by season (see Table 4). Deficiency was greatest in winter at 23%, with a further 26% insufficient. In contrast, deficiency was lowest in summer at 8%, with an additional 16% insufficient. The locations with the lowest 25(OH)D were; Dublin 1 (45.5 ± 31.4 nmol/L), Dublin 11 (46.1 ± 27.3 nmol/L), Lucan (46.5 ± 30.8 nmol/L) and Dublin 8 (49.1 ± 31.9 nmol/L). The locations with the highest 25(OH)D were Dublin 14/16 (59.9 ± 30.8 nmol/L), Dublin 4 (58.8 ± 33.0 nmol/L), Dublin 6/6W (58.6 ± 31.1 nmol/L).

Table 4. 25(OH)D status by area and season.

General Area	N	GM Mean (SD)	Winter			Spring			Summer			Autumn		
			n	<30%	30–49%	*n*	<30%	30–49%	*n*	<30%	30–49%	*n*	<30%	30–49%
Dublin 1	290	45.5 (31.4)	76	37	25	88	26	28	66	9	14	60	30	13
Dublin 2	639	49.5 (29.6)	157	34	20	170	21	29	151	9	25	161	19	22
Dublin 3	219	54.9 (33.5)	52	27	23	61	15	21	50	2	22	56	11	38
Dublin 4	662	58.8 (33.0)	132	19	23	181	21	23	169	7	13	180	10	15
Dublin 5	111	54.6 (30.7)	26	8	42	35	17	31	25	16	12	25	12	16
Dublin 6/6W	5273	58.6 (31.1)	1093	19	25	1488	17	22	1256	6	15	1436	8	17
Dublin 7	496	51.4 (31.5)	88	34	27	133	23	27	150	14	12	125	10	22
Dublin 8	2915	49.1 (31.9)	661	28	25	780	27	26	727	12	20	747	17	24
Dublin 9	173	51.0 (29.5)	49	24	29	41	22	32	41	0	22	42	14	21
Dublin 10	846	50.8 (30.5)	173	32	26	210	24	27	235	8	21	228	11	19
Dublin 11	142	46.2 (27.3)	33	39	39	39	18	41	41	12	20	29	17	17
Dublin 12	3375	54.1 (31.8)	734	22	24	1018	22	24	814	9	15	809	12	17
Dublin 13/17	107	52.0 (35.9)	26	23	27	34	24	35	23	4	22	24	17	13
Dublin 14/16	4129	59.9 (30.8)	924	18	23	1181	13	26	963	6	12	1061	8	16
Dublin 15	480	50.3 (31.5)	111	23	28	129	26	29	126	13	20	114	17	17
Dublin 18	372	54.0 (36.9)	84	21	30	106	25	27	75	7	19	107	6	21
Dublin 20	1353	54.3 (29.8)	335	24	25	384	15	28	319	7	20	315	13	21
Dublin 22	719	49.8 (29.5)	129	28	32	218	24	26	202	11	19	170	18	25
Dublin 24	750	52.3 (30.1)	157	25	30	210	24	24	190	10	12	193	12	21
North Co. Dublin	220	50.7 (27.7)	44	36	39	66	18	23	64	5	25	46	13	20
South Co. Dublin	616	55.9 (29.7)	133	23	26	175	13	29	158	6	17	150	12	18
Lucan, Co. Dublin	5008	46.5 (30.8)	1112	32	27	1353	28	28	1204	15	20	1339	18	22
North Co. Kildare	5734	56.1 (27.5)	1329	18	30	1712	18	26	1249	4	15	1444	6	20
Rest of Kildare	757	56.5 (29.0)	170	23	27	215	14	27	166	4	16	206	9	19
Co. Meath	502	56.2 (31.3)	132	22	25	141	19	23	104	5	14	125	6	25
Co. Wicklow	164	58.2 (28.8)	36	33	19	36	11	19	40	0	8	52	10	21
Rest of Leinster	209	54.1 (29.9)	52	27	29	66	17	36	49	6	14	42	2	19
Rest of Ireland	205	53.8 (30.5)	53	25	28	51	16	29	34	9	18	67	10	24
Total	36,466	53.8 (30.8)	8101	23	26	10,321	20	26	8691	8	16	9353	11	20

In winter, most locations had a prevalence of deficiency of 20% or more. In particular, in this season the areas (D1, D2, D7, D10, D11, Lucan, North County Dublin) and County Wicklow had more than 30% who were deficient. A select number of locations (D4, D6, D6W, D14/D16, North Kildare) had a deficiency of 11–20% in winter while no areas had a prevalence of less than 10%. In summer, some areas had no deficiency (County Wicklow/Dublin 9) while in others such as Dublin 5 the prevalence was as high as 16%.

A geomap gives a visual representation of the prevalence of deficiency by location in the summer and winter (Figure 3, 4). This highlights a widespread deficiency in Dublin (20- >30%) and surrounding counties in the winter (Figure 3). However, the opposite is true in the summer where most areas have a prevalence of deficiency less than 10% (Figure 4).

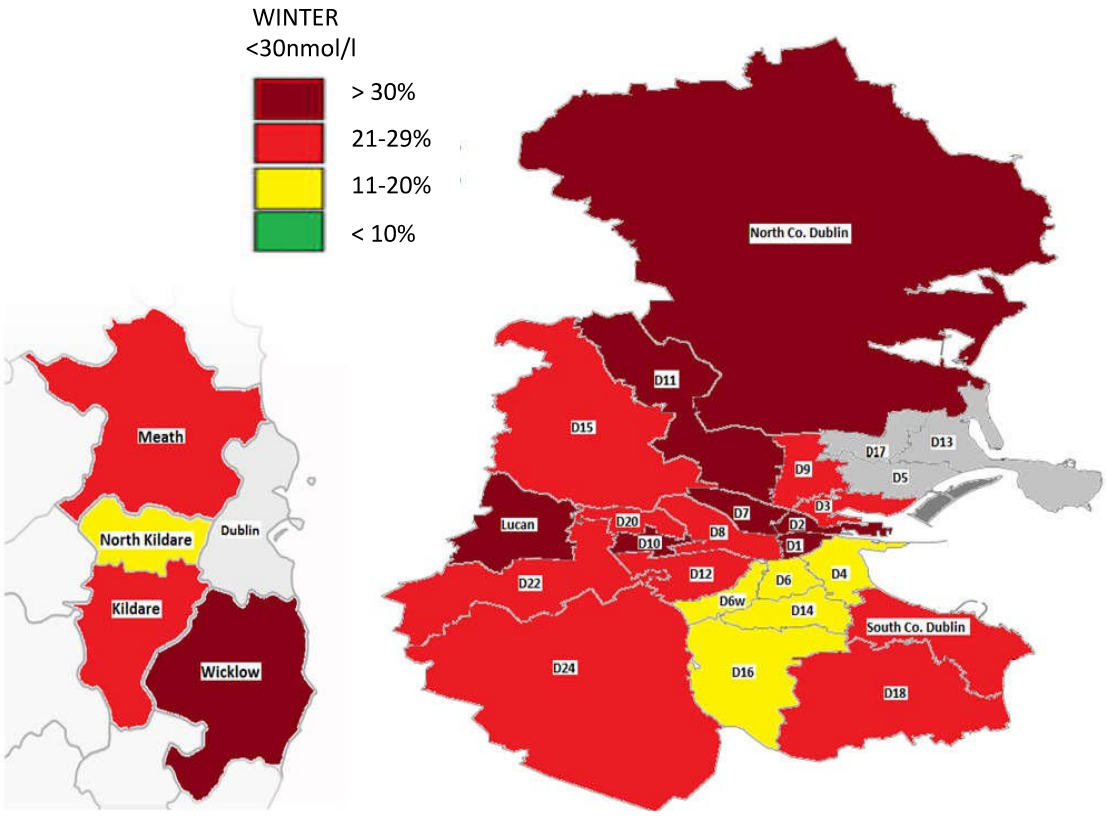

Figure 3. Geomap of 25(OH)D status in Dublin and surrounding counties in winter. Areas with insufficient numbers (<120) for analysis are shown in grey.

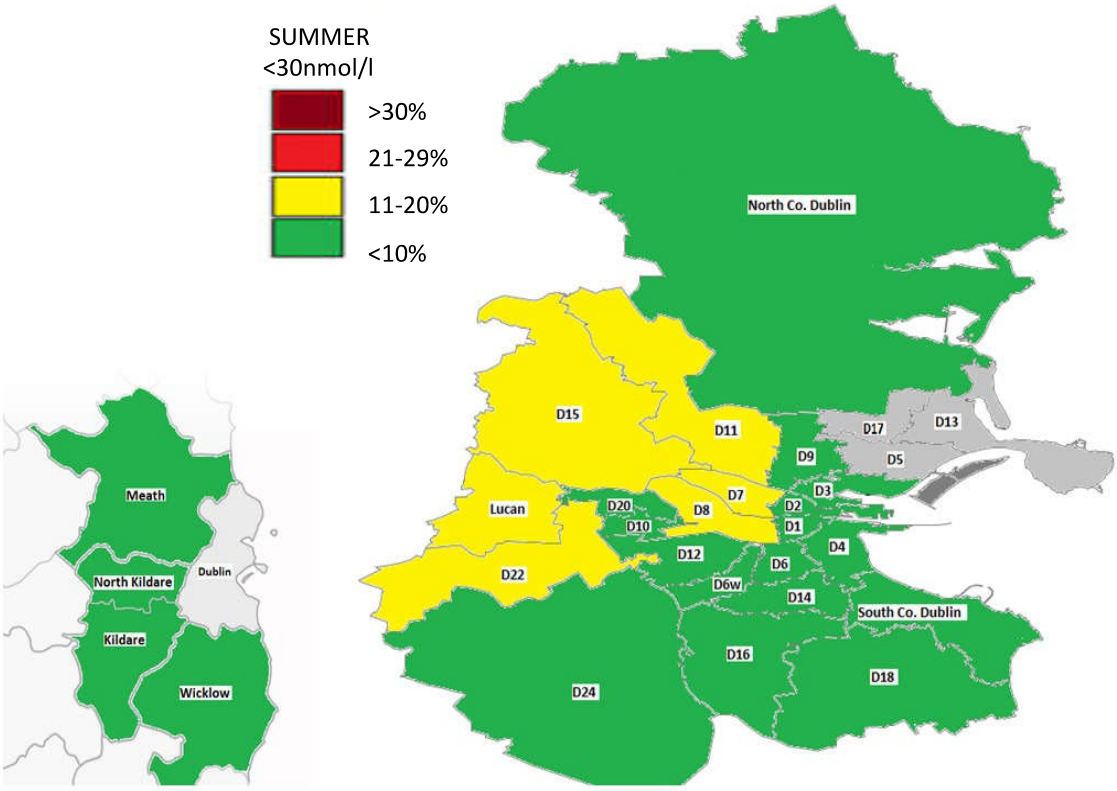

Figure 4.—Geomap of 25(OH)D status in Dublin and surrounding counties in summer. Areas with insufficient numbers (<120) for analysis are shown in grey.

3.4. 25(OH)D Status by Area—Age and Gender

There were significant differences in 25(OH)D status when dichotomised by age across the areas (Table 5). In every area, deficiency was more prevalent in those who were younger (<50 years), with this being more marked in some locations. For example, in Lucan, Dublin 1, Dublin 8 and Dublin 22, more than 20% of those aged <50 were deficient. Similarly, in the same areas and also in Dublin 11 more than 50% of this age group had a level below 50 nmol/L. Conversely, in those aged ≥50 only two areas, Dublin 13/17 and Dublin 2, had a level of deficiency and insufficiency above 20%. In just over half of the locations, males were more likely to be deficient, in keeping with the overall study findings. The prevalence of 25(OH)D > 125 nmol/L ranged from 1–7% in females, to 0–4% in males and was greatest (7%) in women living in Dublin 3.

Table 5. 25(OH)D Status by location, age and gender.

	Age							Gender						
	<50 Years			>50 Years				Female			Male			
Vitamin D (%)	**<30**	**30–49**	**>125**	**<30**	**30–49**	**>125**	***p*-Value**	**<30**	**30–49**	**>125**	**<30**	**30–49**	**>125**	***p*-Value**
Dublin 1	26	21	2	17	28	6	0.420	22	22	3	32	23	1	0.547
Dublin 2	17	27	3	22	25	2	0.140	17	28	3	21	23	2	0.611
Dublin 3	14	30	6	4	21	6	0.025 *	11	23	7	14	45	2	0.009 *
Dublin 4	14	21	3	12	16	6	0.036 *	12	17	5	16	25	3	0.004 *
Dublin 5	11	29	4	18	21	0	0.046 *	9	24	4	23	38	0	0.555
Dublin 6/6W	15	24	3	9	18	4	<0.001 *	11	19	5	15	26	2	<0.001 *
Dublin 7	18	26	4	12	13	4	0.672	16	23	5	19	24	2	0.001 *
Dublin 8	23	27	2	14	21	4	0.002 *	19	24	3	24	27	2	<0.001 *
Dublin 9	14	26	5	10	35	0	0.466	12	26	4	17	36	0	0.549
Dublin 10	18	24	3	16	24	2	0.291	16	23	3	20	26	2	0.349
Dublin 11	19	34	2	15	20	5	0.994	18	33	2	19	31	3	0.211
Dublin 12	18	26	2	14	18	3	<0.001 *	15	20	3	18	26	1	<0.001 *
Dublin 13/17	16	26	6	26	21	0	0.962	18	27	5	17	21	4	0.645
Dublin 14/16	13	26	2	9	17	5	<0.001 *	10	18	5	12	25	1	<0.001 *
Dublin 15	20	29	3	10	16	3	0.656	17	25	4	18	28	1	0.001 *
Dublin 18	16	25	3	10	23	6	0.068	14	20	4	16	32	4	0.042 *
Dublin 20	16	28	2	13	23	3	<0.001 *	14	23	4	14	28	1	<0.001 *
Dublin 22	23	28	2	13	23	4	0.005 *	18	22	3	20	34	2	<0.001 *
Dublin 24	22	26	2	9	17	2	0.004 *	15	21	2	21	27	3	<0.001 *
North Co. Dublin	17	26	2	10	32	0	0.215	17	26	1	9	30	4	0.214
South Co. Dublin	13	27	1	10	19	4	0.254	10	25	3	17	22	2	0.021 *
Lucan, Co. Dublin	27	28	2	12	21	3	<0.001 *	21	24	2	25	28	1	<0.001 *
North Co. Kildare	14	28	2	8	20	3	<0.001 *	10	23	2	12	26	2	<0.001 *
Rest of Kildare	16	25	3	8	21	3	0.303	12	22	3	11	26	2	<0.001 *
Co. Meath	14	27	3	8	17	3	0.328	11	24	3	17	22	2	0.009 *
Co. Wicklow	16	18	2	6	19	3	0.329	9	20	2	19	15	4	0.350
Rest of Leinster	16	28	1	7	25	4	0.521	13	25	3	14	32	0	0.167
Rest of Ireland	14	30	4	9	20	4	0.052	10	28	5	20	28	3	0.425
Total	18	27	2	11	19	4		14	22	3	17	27	2	

Notes: Vitamin D categories expressed as % for <30 nmol/L, 30–49 nmol/L, >125 nmol/L.(*) Indicates significance p <0.05 level.County abbreviated as Co.

3.5. Determinants of Vitamin D Deficiency and Sufficiency

The independent effects of gender, season and location on 25(OH)D status are outlined in Table 6. Season was the strongest predictor of deficiency followed by geographical area and then gender. Those sampled in the winter versus the summer were over four-times more likely to be deficient (OR 4.43, $p < 0.001$). In terms of location, those living in north Dublin versus outside Dublin were more likely to be deficient (OR 1.54, $p < 0.001$) and insufficient (OR 1.089, $p < 0.001$) while those in west Dublin were more than twice as likely to be deficient (OR 2.17, $p < 0.001$). We also identified that females were 32% less likely to be deficient (OR 0.68, $p < 0.001$).

Table 6. Predictors of vitamin D deficiency <30 nmol/L) and insufficiency (30–49 nmol/L) in multinomial regression.

Deficient vs. Sufficient	*n*	B (SE)	OR	Lower	Upper	Effect (%)	*p*-Value
Intercept		1.224 (0.072)					
Age	36,466	0.023 (0.001)	0.977	0.976	0.979	−2	<0.001 *
Female	26,161	0.39 (0.033)	0.677	0.634	0.723	−32	<0.001 *
Winter	8101	−1.49 (0.049)	4.435	4.030	4.881	344	<0.001 *
Spring	10,321	−1.275 (0.048)	3.58	3.261	3.930	258	<0.001 *
Autumn	8691	−0.418 (0.052)	1.519	1.372	1.681	52	<0.001 *
North Dublin	1758	−0.431 (0.076)	1.539	1.327	1.786	54	<0.001 *
South Dublin	18,827	−0.35 (0.043)	1.419	1.304	1.543	42	<0.001 *
West Dublin	8310	−0.776 (0.047)	2.172	1.981	2.382	117	<0.001 *
Outside Dublin	7571						
Insufficient vs. Sufficient							
Intercept		0.479 (0.058)					
Age	36,466	0.017 (0.001)	0.983	0.982	0.985	−2	<0.001 *
Female	26,131	0.387 (0.029)	0.679	0.642	0.719	−32	<0.001 *
Winter	8101	−0.888 (0.04)	2.430	2.247	2.628	143	<0.001 *
Spring	10,321	−0.807 (0.038)	2.241	2.081	2.414	124	<0.001 *
Autumn	8691	−0.264 (0.04)	1.303	1.205	1.408	30	<0.001 *
North Dublin	1758	−0.085 (0.066)	1.089	0.957	1.239	9	<0.001 *
South Dublin	18827	−0.019 (0.034)	1.019	0.953	1.089	2	0.194
West Dublin	8310	−0.256 (0.039)	1.291	1.195	1.395	29	0.586
Outside Dublin	7571						

Notes: (*) Indicates significance at <0.05 level.

3.6. 25(OH)D Status Versus Season, Dichotomised by Age and Gender

The seasonality of 25(OH)D is shown in Figure 5 where the geometric mean for each season over 5 years is illustrated. Seasonality was similar regardless of age or gender. However, 25(OH)D is consistently higher for those over 50 (mean difference + 10.9 nmol/L) and females (mean difference + 5.5 nmol/L) across all seasons (Figure 6, 7).

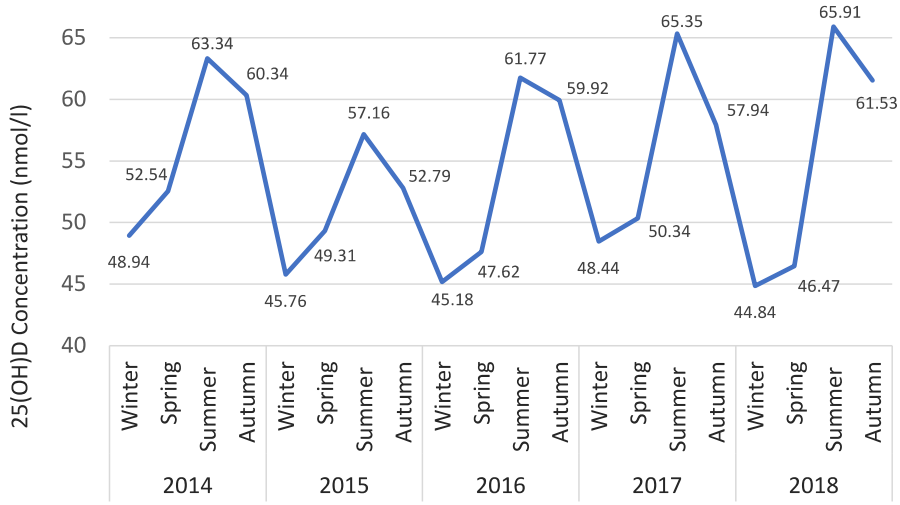

Figure 5. 25(OH)D status versus season.

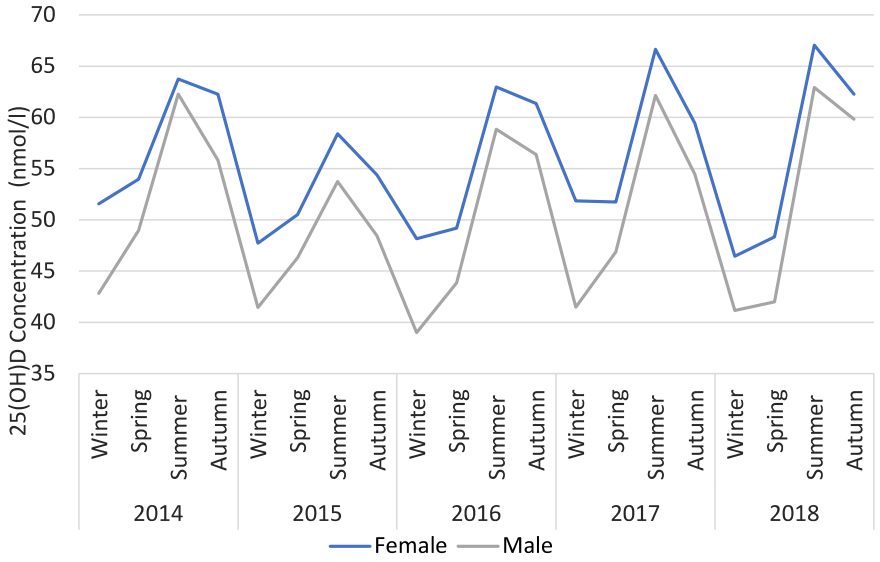

Figure 6. 25(OH)D status versus season, dichotomised by gender.

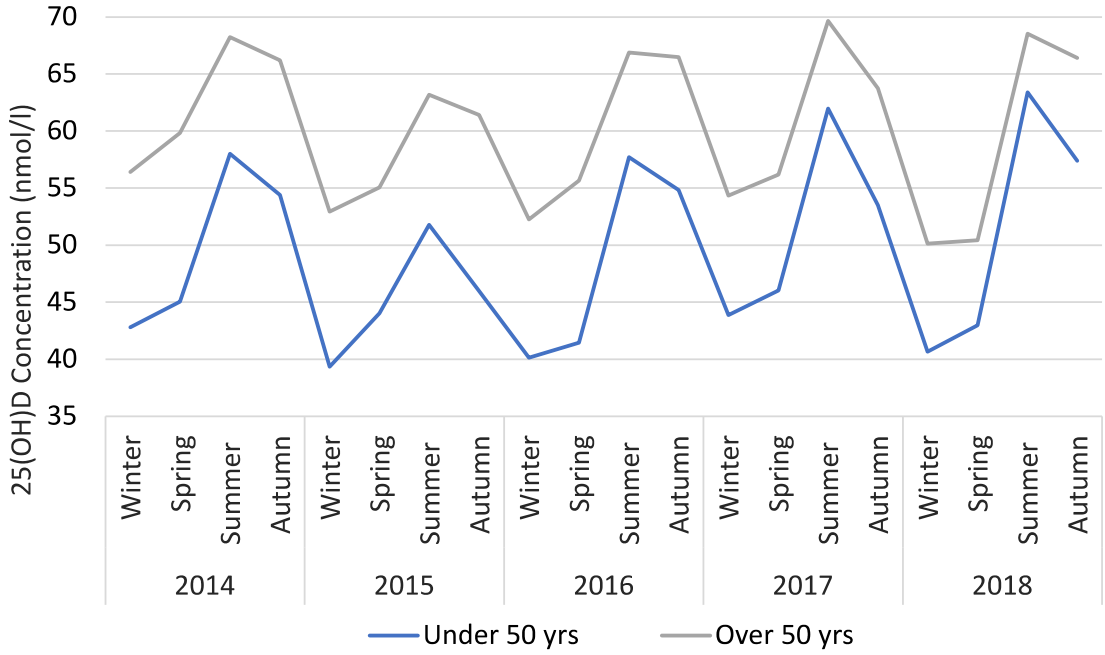

Figure 7. 25(OH)D status versus season, dichotomised by age.

3.7. Cluster Analysis of Differences in 25(OH)D Between Areas (See Supplementary Data and Figures)

Cluster maps of postcodes with significant mean differences in 25(OH)D in the winter (Figure S1) and summer (Figure S2) were created. There were more areas with significant mean differences in the winter (Table S1 and S2). In winter, higher mean 25(OH)D were identified in the areas (D4, D6/6W, D14/16) with significantly lower levels in central (D1, D2, D8), west (D10, D22, Lucan) and north Dublin (North Co. Dublin, D11). In summer, the areas D4, D6/6W and D14/16 had higher status versus Dublin city and west Dublin. Finally, North Kildare had a higher 25(OH)D in the summer compared with the areas of Lucan and Dublin 8 and this also remained the case versus Lucan in the winter.

4. Discussion

To our knowledge this is the largest geomapping study of vitamin D status in Europe. We observed that nearly one in six (15%) of a GP primary care tested-population in Dublin and surrounding areas were vitamin D deficient, rising to one in four (23%) in the winter. Furthermore, an additional 26% were insufficient (30–49 nmol/L), with nearly half of those tested having 25(OH)D levels <50 nmol/L in the winter. We also identified major differences in the prevalence of deficiency between Dublin postal code areas, despite being in close proximity to each other, as well as in other counties. This is concerning as it suggests that a significant proportion of Dublin and surrounding area population have inadequate 25(OH)D status.

4.1. Vitamin D Status by Gender

We observed that overall, females had higher vitamin D serum levels across all age groups, similar to other studies [14,15,23]. In fact, females were about a third (32%) less likely to be deficient. Some research conflicts with this [24,25] although a meta-analysis of 394 studies (n = 33,266) discovered higher mean 25(OH)D in women, with levels comparable to our study [26]. In about half of locations the difference in 25(OH)D between genders was not statistically significant, but the analysis may have been underpowered due to smaller sample sizes in some areas. In addition, other factors related to gender which we were not able to adjust for might account for this.

The majority of vitamin D requests (72%) were for females, a finding which has been reported elsewhere [15,19]. Females may be more likely to attend their GP and partake in positive health behaviours [27]. They are also more likely to take a dietary supplement [28]. For example, in one study, females (particularly those aged over 50) were more than twice as likely to routinely take a vitamin supplement [29,30]. Furthermore, there is a greater awareness of the importance of bone health in women, where osteoporosis is more prevalent and emphasis is placed on prevention and treatment [31].

4.2. Vitamin D Status by Age

Those who were younger (<50 years) had lower vitamin D status. This did not change over the 5-year period, with about 1 in 5 of those aged < 50 being deficient compared to 1 in 10 over 50. Surprisingly, those aged between 18 and 39 years had the same prevalence of deficiency (21%) as the oldest age group (+90 years). This nadir in 25(OH)D in young adults was also found in the similarly located northern latitude (51° N) city of Calgary, Alberta [18]. A 'U'-shaped distribution of vitamin D deficiency in the youngest and oldest adults has likewise been described in the west of Ireland [15], Romania [32], and São Paulo, Brazil [33].

One reason why younger adults may be deficient is that they may spend more time indoors e.g., in their working environment. A study by Sowah et al., 2017 found that shift workers, healthcare and indoor workers have a higher risk of deficiency due to a lack of opportunity for sunshine exposure [12]. Another factor in younger adults may be the difference in dietary intake of vitamin D. In a recent Irish dietary survey, it was estimated that 19.2% of the population are now vegan, vegetarian or seeking to reduce dietary animal products with the majority of those being younger (aged 18–34) [34]. This may be a cause for concern as meat is the largest contributor of vitamin D in adults under 65, accounting for a third of total dietary intake [35]. Moreover, when compared to those over 65, the proportion of adults who did not meet the recommended dietary intake at that time (5 μg/day) was greater in the age group (18–64) for both males (72% vs. 59%) and females (78% vs. 58%) [35].

Ensuring adequate vitamin D status in younger adults is important, as peak bone mass is acquired in the early-to-late twenties [36]. Suboptimal 25(OH)D earlier in life and over prolonged periods might also contribute to other adverse health outcomes as consistent with the theory of 'long latency deficiency disease' [37]. For example, vitamin D deficiency has been associated with upregulation of inflammatory markers, endothelial dysfunction and chronic, low-grade inflammation that may increase the risk of cardiovascular disease as well as mortality from cancer and other causes [38,39].

Our findings demonstrate that 25(OH)D peaked in the decade 60–69 years in which most people retire and may reflect more time spent outdoors [40]. Conversely, 25(OH)D levels declined from the age of 70 onwards. This may largely relate to increasing frailty and less sunshine exposure. However, reduction in the capacity of the skin to synthesize vitamin D by up to 75% with age may also help to explain this [41]. In addition, sequestration of vitamin D within increased body fat with ageing as well as reduced dietary intake may contribute [42]. Furthermore, poor compliance with vitamin D supplements in older adults, especially in those where there is polypharmacy may also be a factor [43].

4.3. Vitamin D Status by Season and Location

A geomap depicting 25(OH)D status in Dublin and the surrounding areas illustrates major variations in the prevalence of deficiency by location. This varied greatly especially in the winter, where it ranged from 18% in areas like Dublin 14/16 and North Co. Kildare to up to >37% in Dublin 1 and Dublin 11. Findings were similar to a previous geomapping study of Vitamin D status in Dublin, although that study focused on a substantially smaller population, did not include as many areas and only covered a one year period [19].

In the winter, we found clusters of areas south Dublin (D4, D6/6W, D14/16) with greater serum 25(OH)D compared to west Dublin, north Dublin and more central Dublin city areas. In fact, these

particular locations in south Dublin are some of the most affluent areas in the county and nationally, as determined by HP (Haase-Pratschke) Pobal Score 2016, a deprivation index of demographic profile, social class composition and labour market situation [44]. Socioeconomic status and 25(OH)D have been closely linked, with those in typically disadvantaged areas having an increased risk of deficiency [18,45]. For example, in the TILDA study of Irish adults, those with lower asset wealth were 1.5-times more likely to be deficient. This may be due to factors linked to lower socioeconomic status including reduced dietary vitamin D intake, less sunny holiday travel and possibly higher rates of obesity and smoking [14,46].

In the summer, most areas had a prevalence of deficiency of less than 10% except locations such as north and west Dublin including Lucan. This may be in part accounted for by a greater proportion of individuals of Asian and Black ethnicity living here [47]. Indeed, those with darker or more pigmented skin have a greater risk of deficiency at locations in northern latitudes [26]. However, overall season had a large impact on 25(OH)D in keeping with those in the winter being over four-times more likely to be deficient versus in the summer [22,48]. Importantly, the extent of the differences in deficiency between areas appeared to be attenuated in the summer, highlighting the importance of sun exposure.

Those living in the areas of north and west Dublin were also more likely to be deficient compared to those living outside Dublin. While we did not define rural or urban areas, locations outside Dublin are less urbanised and some are rural. These findings are in contrast to a study by Griffin et al., 2019, which found that Irish urban dwellers had higher 25(OH)D and lower rates of deficiency [15]. However, these differences might be accounted for by local variations in socioeconomic status and ethnicity.

There was no improvement in vitamin D status over a five-year period despite increased testing and greater awareness [1]. This suggests that a large proportion of the population have inadequate 25(OH)D but have not yet been identified. As the list of potential comorbidities related to vitamin D expands beyond bone and muscle health, it is important that no subgroup of the population is left vulnerable to deficiency. For example, vitamin D may help to maintain immune function, reduce the risk of respiratory infections and downregulate inflammatory cytokines, suggesting that deficiency could have a negative impact on Covid-19 outcomes [40,49]. Furthermore, vitamin D is a known regulator of cardiovascular and renal function mediated via the interaction of Vitamin D receptors within the renin-angiotensin-aldosterone system (RAAS), highlighting the multisystemic effects of vitamin D deficiency [50].

We did find that a small (1–7%) but not insignificant proportion of our study population had 25(OH)D levels >125 nmol/L, particularly females over 50 who may be more likely to take prescribed or over-the-counter vitamin D. While a similar prevalence (>125 nmol/L) has been identified elsewhere [22], it is important that any future Irish guidance on vitamin D intake takes into account the potential for inadvertently increasing the risk of hypervitaminosis D.

There are no national Irish guidelines regarding vitamin D testing, and recommendations for supplementation are limited to infants. This study highlights the presence of vulnerable groups with vitamin D deficiency, including males and young adults, living in poorer socioeconomic areas. Furthermore, our geomap and cluster analysis highlights locations where the prevalence of deficiency is significantly higher. These findings provide valuable information for GPs and public health bodies in developing strategies for targeted interventions to optimise vitamin D status.

4.4. Strengths of Study

The primary strength of this study was its large population size and the novel use of a geomap to gain a visual representation of vitamin D status in a large city and its surrounding areas. In fact, to our knowledge, this is the largest study in Europe to geomap vitamin D and includes data collected over a 5-year period. We used the gold standard for vitamin D assessment; LC-MS/MS, NIST internal standard and are DEQAS accredited to ensure accuracy.

4.5. Limitations of Study

Our study was based on GP vitamin D requests and this limits the generalisability of the findings to a wider population. In particular, there is likely to be selection bias in testing with study participants having medical conditions or other factors putting them at risk of deficiency. However, unlike other studies we minimised the potential for this by not including vitamin D samples received from outpatient or acute hospital services and also excluded those from institutionalised adults.

We were not able to adjust for several factors that influence 25(OH)D including biophysical (BMI, skin type, medical conditions e.g., malabsorption syndromes) and lifestyle (supplementation, smoking, sun exposure, alcohol intake, diet, education). Finally, our study was cross-sectional and therefore we could not make any direct inferences as to the causality of factors influencing vitamin D status.

5. Conclusions

This study shows that nearly one in four of the GP-tested population in Dublin and surrounding areas are vitamin D deficient in the winter, during which time up to 50% have 25(OH)D less than 50 nmol/L. Moreover, those living in poorer socioeconomic areas were more likely to be deficient, as are males, younger (18–39 years) and older adults (80+ years). This study identifies key groups at risk of vitamin D deficiency and provides important public health information for the targeting of interventions to optimise vitamin D status. Our data indicate that inadequate vitamin D status is not just limited to older adults, but it is widespread across many population groups. This highlights the importance for recommendations for vitamin D intake to include the entire population and/or mandatory vitamin D food fortification.

Supplementary Materials: the following are available online at www.mdpi.com/xxx/s1, Figure S1: Cluster map analysis in winter, Figure S2: Cluster map analysis in summer, Table S1: Condensed Pairwise ANOVA Winter. All mean difference is significant at the <0.05 level, Table S2: Condensed Pairwise ANOVA Summer. All mean difference is significant at the 0.05 level.

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Conflicts of Interest: the authors declare no conflict of interest.

Appendix A

Table A1. Pairwise ANOVA Winter.

General Area	General Area	Mean (SE)	Sig.	95% Confidence Interval	
				Lower	Upper
Dublin 1	Dublin 4	−19.3 (4.3)	0.003	−35.7	−2.8
	Dublin 6/6W	−15.6 (3.6)	0.004	−29.2	−2.0
	Dublin 14/16	−17.2 (3.6)	0.001	−30.8	−3.5
Dublin 2	Dublin 14/16	−10.8 (2.6)	0.011	−20.7	−0.9
Dublin 4	Dublin 1	19.3 (4.3)	0.003	2.7	35.7
	Dublin 10	15.1 (3.5)	0.006	1.8	28.3
	Dublin 11	25.9 (5.8)	0.004	3.6	48.2
	North Co. Dublin	21.8 (5.2)	0.011	1.8	41.7
	Lucan, Co. Dublin	13.9 (2.7)	<0.001	3.4	24.5
Dublin 6/6W	Dublin 1	15.6 (3.6)	0.004	2.0	29.2

	Dublin 8	6.5 (1.5)	0.004	0.9	12.2
	Dublin 10	11.4 (2.5)	0.001	2.0	20.9
	Dublin 11	22.3 (5.3)	0.010	2.0	42.5
	North Co. Dublin	18.2 (4.6)	0.031	0.5	35.8
	Lucan, Co. Dublin	10.3 (1.3)	<0.001	5.5	15.2
Dublin 8	Dublin 6/6W	−6.5 (1.5)	0.004	−12.2	−0.9
	Dublin 14/16	−8.0 (1.5)	<0.001	−13.9	−2.2
Dublin 10	Dublin 4	−15.0 (3.5)	0.006	−28.3	−1.8
	Dublin 6/6W	−11.4 (2.5)	0.001	−20.8	−2.0
	Dublin 14/16	−12.9 (2.5)	<0.001	−22.4	−3.4
Dublin 11	Dublin 4	−25.9 (5.8)	0.004	−48.2	−3.6
	Dublin 6/6W	−22.3 (5.3)	0.010	−42.5	−2.0
	Dublin 14/16	−23.8 (5.3)	0.003	−44.1	−3.5
Dublin 12	Lucan, Co. Dublin	7.3 (1.4)	<0.001	1.8	12.7
Dublin 14/16	Dublin 1	17.2 (3.6)	0.001	3.5	30.8
	Dublin 2	10.8 (2.6)	0.011	0.9	20.7
	Dublin 8	8.0 (1.5)	<0.001	2.2	13.9
	Dublin 10	12.9 (2.5)	<0.001	3.4	22.4
	Dublin 11	23.8 (5.3)	0.003	3.5	44.0
	Dublin 22	11.7 (2.8)	0.012	0.9	22.5
	North Co. Dublin	19.7 (4.6)	0.008	2.0	3.4
	Lucan, Co. Dublin	11.9 (1.3)	<0.001	68	17.0
Dublin 22	Dublin 14/16	−11.7 (2.8)	0.012	−22.5	−0.9
North Co. Dublin	Dublin 4	−21.8 (5.2)	0.011	−41.7	−1.8
	Dublin 6/6W	−18.2 (4.6)	0.031	−35.8	−0.5
	Dublin 14/16	−19.7 (4.6)	0.008	−37.4	−2.0
Lucan, Co. Dublin	Dublin 4	−14.9 (2.8)	<0.001	−24.5	−3.4
	Dublin 6/6W	−10.3 (1.3)	<0.001	−15.2	−5.5
	Dublin 12	−7.3 (1.4)	<0.001	−12.7	−1.8
	Dublin 14/16	−11.87 (1.3)	<0.001	−17.0	−6.8
	North Co. Kildare	−7.4 (1.2)	<0.001	−12.0	−2.7
North Co. Kildare	Lucan, Co. Dublin	7.4 (1.2)	<0.001	2.7	12.1

Table A2. Pairwise ANOVA Summer.

General Area	General Area	Mean (SE)	Sig.	95% Confidence Interval	
				Lower	Upper
Dublin 2	Dublin 14/16	−12.0 (2.6)	0.001	−21.7	−2.2
Dublin 4	Dublin 8	9.8 (2.5)	0.033	0.3	19.3
	Lucan, Co. Dublin	13.2 (2.4)	<0.001	4.0	22.3
Dublin 6/6W	Dublin 8	6.1 (1.4)	0.003	0.93	11.3
	Lucan, Co. Dublin	9.5 (1.1)	<0.001	5.0	14
Dublin 7	Dublin 14/16	−11.0 (2.6)	0.006	−20.8	−1.2
Dublin 8	Dublin 4	−9.8 (2.5)	0.033	−19.3	−0.3
	Dublin 6/6W	−6.1 (1.4)	0.003	−11.3	−0.9
	Dublin 14/16	−10.1 (1.4)	<0.001	−15.6	−4.6
	North Co. Kildare	−6.4 (1.4)	0.001	−11.6	−1.2
Dublin 10	Dublin 14/16	−8.1 (2.1)	0.046	−16.2	−0.0
Dublin 12	Lucan, Co. Dublin	9.0 (1.3)	<0.001	3.9	14.0
Dublin 14/16	Dublin 2	12.0 (2.6)	0.001	2.2	21.7
	Dublin 7	11 (2.56)	0.006	1.2	20.8
	Dublin 8	10.1(1.4)	<0.001	4.6	15.5
	Dublin 10	8.1 (2.1)	0.046	0.04	16.2
	Dublin 22	9.4 (2.3)	0.013	0.7	18.0
	Lucan, Co. Dublin	13.4 (1.3)	<0.001	8.7	18.3
Dublin 20	Lucan, Co. Dublin	8.6 (1.8)	0.001	1.5	15.6
Dublin 22	Dublin 14/16	−9.4 (2.3)	0.013	−17.8	−0.7
Lucan, Co. Dublin	Dublin 4	−13.2 (2.4)	<0.001	−22.3	−4.0

	Dublin 6/6W	−9.5 (1.2)	<0.001	−14	−5.0
	Dublin 12	−9.0 (1.3)	<0.001	−14.0	−3.9
	Dublin 14/16	−13.5 (1.3)	<0.001	−18.3	−8.7
	Dublin 20	−8.6 (1.8)	0.001	−15.6	−1.5
	North Co. Kildare	−9.8 (1.2)	<0.001	−14.3	−5.3
	Rest of Kildare	−10.9 (2.4)	0.002	−20.1	−1.7
North Co. Kildare	Dublin 8	6.4 (1.4)	0.001	1.2	11.6
	Lucan, Co. Dublin	9.8 (1.2)	<0.001	5.3	14.3
Rest of Kildare	Lucan, Co. Dublin	10.9 (2.4)	0.002	1.7	20.1

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Chapter 4: Vitamin D retesting by General Practitioners: A Factor and Cost Analysis

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Helena Scully*, Eamon Laird, Martin Healy, Vivion Crowley, James Bernard Walsh and Kevin McCarroll

Vitamin D retesting by general practitioners: a factor and cost analysis

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Abstract

Objectives: Vitamin D testing by Primary Care doctors is increasing, placing greater workloads on healthcare systems. There is little data though on vitamin D retesting in Ireland. This study aims to investigate the factors associated with vitamin D retesting by Irish General Practitioners (GPs) and examine the resulting costs.

Methods: This is a retrospective analysis over 5 years (2014–2018) of GP requested 25-hydroxyvitamin D (25(OH) D) results in 36,458 patients at a major city hospital in Dublin, Ireland. Those with one test were compared with individuals who were retested and samples categorised to determine changes in status between tests.

Results: Nearly one in four patients (n=8,305) were retested. Positive predictors of retesting were female ($p<0.001$), age (60–69 years, $p<0.001$), location (Co. Kildare, $p<0.001$) and initial deficiency (<30 nmol/L, $p<0.001$) or insufficiency (30–49.9 nmol/L, $p<0.001$). Vitamin D status improved on retesting, with deficiency halving on first retest (9 vs. 18%, $p<0.001$) and dropping to 6% on further retests. About 12.2% of retests were done within 3 months and 29% had ≥2 retests within 1 year. 57% of retests were in those initially vitamin D replete (>50 nmol/L). The annual cost of inappropriate testing was €61,976.

Conclusions: One in four patients were retested and this varied by age, gender and patient location. Over 10% of retests were inappropriately early (<3 months), a third too frequent and over half were in replete individuals incurring significant costs. Clear guidance for GPs on minimum retesting intervals is needed, as well as laboratory ordering systems to limit requests using pre-defined criteria.

Keywords: 25(OH)D; retesting; testing trends; vitamin D.

***Corresponding author: Helena Scully**, Mercers Institute for Research on Ageing, St James's Hospital, Dublin 8, Ireland,
E-mail: Scullyhe@tcd.ie. https://orcid.org/0000-0002-1641-1766
Eamon Laird, School of Medicine, Trinity College Dublin, Dublin, Ireland
Martin Healy and Vivion Crowley, Department of Biochemistry, St James's Hospital, Dublin, Ireland
James Bernard Walsh and Kevin McCarroll, Mercers Institute for Research on Ageing, St James's Hospital, Dublin, Ireland

Introduction

Vitamin D is a fat soluble secosteroid predominantly obtained by endogenous synthesis via the action of Ultraviolet-B (UV-B) light on skin. Between October and March, populations above 40° north cannot produce meaningful vitamin D, and rely solely on dietary sources [1]. Vitamin D has an established role in bone and muscle health with deficiency causing rickets in children, osteomalacia and osteoporosis in adults [1]. Deficiency is associated in non-skeletal conditions including cardiovascular [2], autoimmune and neurological disease [3], diabetes [4], inflammation [5], respiratory infections [6] and depression [7], though evidence for causality is lacking. The Irish population is at-risk of vitamin D deficiency (<30 nmol/L) due to its northern latitude (50–55°N), effecting about 15% of Irish adults [8, 9], with up to 40–60% insufficient (<50 nmol/L) [9–11].

In Ireland, there has been a substantial increase in vitamin D testing in the last decade [12], with a 37% rise in requests between 2014 and 2018 [8], consistent with an observed global surge [13]. Testing in the UK has increased 50-fold between 2005 and 2015 [14]. Varying increases have been identified elsewhere, with a four-fold increase in Canada [15], 7.5-fold in France [16] and 94-fold in Australia [17] over a similar period. In Denmark, testing rose from one in 500 inhabitants in 2004, to one in five in 2010 [18], while in the US it was a top five most requested test, costing $350 million in 2017 [19]. This increase may be related to greater public awareness and media interest in vitamin D and its potential, but unproven, benefits beyond bone health [13]. Currently, Ireland is lacking data on the appropriateness of vitamin D testing, including clinical indications and retesting prevalence in primary care.

There are numerous guidelines by various organisations regarding indications for vitamin D testing [20, 21]. Most focus on criteria for initial testing, with different

recommendations on when to retest [21–23]. The Royal Osteoporosis Society advises monitoring is generally unnecessary but may be appropriate for symptomatic vitamin D deficiency or malabsorption or where poor compliance is suspected [21]. In the UK, despite recommendations, inappropriate testing accounted for 70–77% of vitamin D tests, with malaise/tiredness contributing between 20 and 30% of tests [24]. Vitamin D testing by General Practitioners' (GPs) for non-specific conditions such as fatigue has been reported in the Netherlands [25]. In Canada, a quarter of vitamin D tests were repeated too early, with undefined clinical indications in many instances [26]. Furthermore, while women are more likely to be vitamin D sufficient compared with men, they are more likely to be tested [14, 27].

In Ireland, the Health Service Executive (HSE) suggests testing for metabolic bone disorders where vitamin D may improve outcomes such as osteoporosis, hyperparathyroidism and Paget's disease [28]. It includes other conditions that might lead to or be attributed to deficiency including malabsorption conditions (coeliac/inflammatory bowel disease), unexplained musculoskeletal symptoms, liver disease and for certain medications (e.g. anti-epileptics) [28]. However, screening for otherwise asymptomatic individuals at-risk of deficiency is not recommend. It also advises against routine retesting but provides no specific criteria for who should be retested.

Presently in Ireland data on vitamin D retesting is limited, including its contributary factors and cost implications. In this study, we aim to explore the predictors of vitamin D retesting by primary care doctors with regard to age, gender, initial status and GP location. Secondly, we will investigate vitamin D status after retesting, and examine costs due to inappropriate requests.

Materials and methods

Data collection

Vitamin D requests (2014–2018) from primary care GPs at St James's hospital (SJH), Dublin Ireland were searched via the biochemistry department information system (iSOFT Telepath®). Exclusion criteria were: aged <18 years, missing/incomplete demographic data, non-community dwelling address (e.g. nursing home or hospital), or address outside the Republic of Ireland. Repeat vitamin D results were identified and coded. Geomapping of patient addresses has previously been completed [8].

Serum 25(OH)D

Serum 25-hydroxyvitamin D 25(OH)D (total 25(OH)D2 and 25(OH)D3), was quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (API 4000; AB SCIEX) using a fully validated method (Chromsystems Instruments and Chemicals GmbH; MassChrom 25-OH-Vitamin D3/D2) at the Biochemistry Department of SJH, which is fully accredited to ISO 15189:2012 standard. Quality is monitored by the vitamin D External Quality Assessment Scheme (DEQAS) and assay of internal quality controls, National Institute of Standards and Technology (NIST) 972 25(OH)D standard reference material (SRM 972). The respective inter- and intra-assay coefficients of variation are 5.7 and 4.5%. We defined deficiency; <30 nmol/L, insufficiency; 30.0–49.9 nmol/L and sufficiency; ≥50 nmol/L [29]. Participants with 25(OH)D level >125 nmol/L were identified. Seasons were defined as winter: (December, January, February); Spring: (March, April, May); Summer: (June, July, August); Autumn: (September, October, November).

Statistics

Analysis was carried out using SPSS (Version 26, IBM Corp., Armonk, NY, USA). Data normality was checked by the Kolmogorov–Smirnov test. Data are reported as geometric mean with standard deviation. Statistical significance ($p<0.05$) was assessed using independent sample t-tests, one way ANOVA for continuous and Chi-squared for categorical variables. Patients were categorised into a baseline cohort (initial vitamin D test but no retests), with retested cohorts divided into; initial test, first retest or ≥2 retests. Determinants of retesting, including age category, gender, geographical area and sampling season was explored using multi-nominal logistic regression. We defined five areas (North, South and West Dublin, Kildare and Rest of Ireland) as previously described [8]; with rest of Ireland as the reference area.

Cost analysis estimated the number of patients needed to test (NNT) to detect one with deficiency, insufficiency, or excess vitamin D (>125 nmol/L) by gender, age and location. The percentage in each vitamin D category was divided into 100 to calculate the NNT. Inappropriate testing costs was estimated, defined as (1) retests within 3 months of the first or initial test, (2) two or more retests within 1 year and (3) retests in those who were initially vitamin D replete (50–75 nmol/L). The calculation was predicated on a laboratory cost of €40 per 25(OH)D sample.

Results

Demographics

Over 5 years, 50,088 serum 25(OH)D tests were reported to GPs after exclusion criteria. There were 36,458 patients in the study, representing 8,305 retested and 28,153 were who were not retested. In the retested cohort, there were 21,935 samples, including 8,305 initial baseline results, 8,305 first retests and 5,325 ≥2 retests. Overall, 22.8% of patients were retested, accounting for 27.2% of vitamin D requests. Retesting numbers was similar between 2014 and 2016 but lower in 2017–2018 (Supplementary Table 1). Baseline demographics of non-retested and retested group are displayed in Table 1.

The retested cohort were more likely to be female (72.4 vs. 71.4%, p=0.047), older (51.6 years ± 16.3 vs. 46.4 years ± 17.7, p<0.001) and live in County Kildare (23.2 vs. 16.2%,

Table 1: Characteristics of study population at baseline (non-retested and retested).

	n	Non-retested n=28,153 n (%)	Retested n=8,305 n (%)	p-Value
25(OH)D[a]	36,458	54.5 (30.2)	51.5 (31.9)	<0.001
<30 nmol/L	5,401	3,917 (13.9)	1,484 (17.8)	<0.001
30–49.9 nmol/L	8,896	6,791 (24.1)	2,105 (25.3)	0.022
>50 nmol/L	22,163	17,445 (62.0)	4,718 (56.8)	<0.001
Female	26,129	20,116 (71.4)	6,013 (72.4)	0.047
Age, years[a]	36,458	46.4 (17.7)	51.6 (16.3)	<0.001
Winter sample, %	14,609	11,330 (40.2)	3,279 (39.5)	0.109
Age category, years	**n**	**n (%)**	**n (%)**	
Age <50	18,962	15,482 (55)	3,480 (42)	<0.001
18–39	11,339	9,573 (34.0)	1,766 (21.3)	<0.001
40–49	6,978	5,428 (19.3)	1,550 (18.7)	0.209
50–59	6,329	4,678 (16.6)	1,651 (19.9)	0.040
60–69	5,750	4,021 (14.3)	1,729 (20.8)	<0.001
70–79	3,854	2,778 (9.9)	1,076 (12.9)	<0.001
80–89	1,990	1,494 (5.3)	496 (5.9)	0.019
>90	218	181 (0.6)	37 (0.4)	<0.001
Districts	**n**	**n (%)**	**n (%)**	
North Co. Dublin	1,758	1,512 (5.4)	246 (3.0)	<0.001
South Co. Dublin	18,817	14,771 (52.5)	4,046 (48.7)	<0.001
West Co. Dublin	8,308	6,442 (22.9)	1,866 (22.5)	0.490
Co. Kildare	6,496	4,571 (16.2)	1,925 (23.2)	<0.001
Rest of Ireland	1,079	857 (3.0)	222 (2.7)	0.080

[a]Indicates results reported as geometric mean (SD). Winter was defined as October–February. Independent sample t-tests for continuous and cross tabulation with chi-squared for categorical variables were used.

p<0.001) but less likely to live in South (48.7 vs. 52.5%, p<0.001) or North Dublin (3.0 vs. 5.4%, p<0.001) vs. the non-retested. The proportion of young people (<50 years) that were retested was smaller (42 vs. 55%, p<0.001). Retesting was more prevalent in those age 50–59 years (19.9 vs. 16.6%, p=0.04), 60–69 years (20.8 vs. 14.3%, p<0.001) and 70–79 years (12.9 vs. 9.9%, p<0.001). The percentage of very old adults (<90 years) was similar between both groups (0.6 vs. 0.4%) albeit the difference statistically significant (p<0.001). There was no difference in the proportion tested in Winter. Vitamin D deficiency at baseline was greater in the retested group (17.8 vs. 13.9%, p<0.001) as was insufficiency (25.3 vs. 24.1%, p=0.022).

Predictors of retesting

The predictors of retesting are shown in Table 2. Deficient and insufficient patients were respectively 70% (Odds Ratio [OR] 1.70, confidence interval [CI] 1.58–1.83, p<0.001) and 28% (OR 1.28, CI 1.21–1.36, p<0.001) more likely to be retested. The other main predictor was age, with those between 18 and 39 years least likely to be retested (OR 0.51, CI 0.47–0.55, p<0.001), followed by those aged >90 years (OR 0.60, CI 0.42–0.86, p=0.005). Location was also a predictor, with those living in North County Dublin (OR 0.68, CI 0.55–0.83, p<0.001) least likely, and those in the Kildare most likely to have a retest (OR 1.46, CI 1.24–1.71, p<0.001). Females were 15% more likely to be retested (OR 1.15, CI 1.09–1.21, p<0.001) as were those who were initially tested in the Summer (OR 1.06, CI 1.01–1.12, p=0.02).

Table 2: Predictors of retesting (on first retest).

Retested vs. not retested	n	B	OR	Confidence interval		p-Value
				Lower	Upper	
Intercept	36,458	−1.34				
Female	26,129	0.14	1.15	1.09	1.21	<0.001
Age, years						
18–39	11,339	−0.68	0.51	0.47	0.55	<0.001
40–49	6,978	−0.24	0.79	0.73	0.85	<0.001
60–69	5,750	0.22	1.25	1.15	1.35	<0.001
70–79	3,854	0.15	1.16	1.06	1.27	0.001
80–89	1,990	0	1.00	0.89	1.13	0.984
>90	218	−0.51	0.60	0.42	0.86	0.005
50–59[a]	6,329					
Location						
North Co. Dublin	1,758	−0.39	0.68	0.55	0.83	<0.001
South Co. Dublin	18,817	−0.08	0.92	0.79	1.08	0.31
West Co. Dublin	8,308	0.01	1.00	0.86	1.18	0.96
Co. Kildare	6,496	0.38	1.46	1.24	1.71	<0.001
Rest of Ireland[a]	1,079					
Vitamin D, nmol/L						
<30	5,401	0.53	1.70	1.58	1.83	<0.001
30–50	8,896	0.25	1.28	1.21	1.36	<0.001
>50[a]	22,161					
Season – summer Winter[a]	21,849	0.06	1.06	1.01	1.12	0.02

[a]Indicates reference variable, analysed using multi-nominal logistic regression. OR, Odds Ratio.

Vitamin D status in retested population

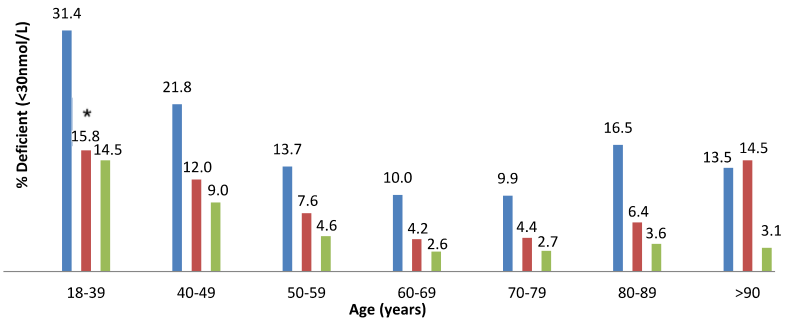
Over half (57%) of retested patients were initially vitamin D replete (>50 nmol/L), with 26% between 50 and 74 nmol/L. Baseline deficiency was more prevalent in retested males vs. females (20 vs. 17%) (Table 3). Mean 25(OH)D increased with each retest, with a larger increment between the initial and first retest (+11.0 nmol/L, p<0.001) vs. first retest and ≥2 retests (4.7 nmol/L, p<0.001). This was identified in both

Table 3: Cohort characteristics of retested patients.

	Initial test 8,305	First retest 8,305	p-Value	≥2 Retests 5,325	p-Value
25(OH)D[a]	51.5 (32.0)	62.5 (31.1)	<0.001	67.2 (30.3)	<0.001
<30 nmol/L, %	18	9	<0.001	6	<0.001
30–49.9 nmol/L, %	25	19	<0.001	17	<0.001
>125 nmol/L, %	3	4	<0.001	5	0.151
Female	6,013	6,013		3,813	
25(OH)D[a]	52.9 (32.7)	64.3 (31.6)	<0.001	68.7 (30.7)	<0.001
<30 nmol/L, %	17	8	<0.001	5	<0.001
30–49.9 nmol/L, %	24	17	<0.001	16	0.013
>125 nmol/L, %	3	5	<0.001	5	0.305
Male	2,292	2,292		1,512	
25(OH)D[a]	47.9 (29.6)	57.8 (29.1)	<0.001	63.6 (29.1)	<0.001
<30 nmol/L, %	20	10	<0.001	6	<0.001
30–49.9 nmol/L, %	28	23	<0.001	19	0.001
>125 nmol/L, %	2	3	0.004	4	0.095
Age categories, years	8,305	8,305		5,325	
18–39[a]	39.8 (31.6)	52.8 (30.6)	<0.001	55.0 (31.4)	0.273
40–49[a]	45.9 (29.9)	56.1 (32.6)	<0.001	59.6 (29.7)	0.133
50–59[a]	54.5 (31.5)	63.4 (30.2)	<0.001	66.2 (30.3)	0.244
60–69[a]	60.7 (30.5)	69.9 (28.8)	<0.001	73.9 (29.0)	0.002
70–79[a]	62.5 (30.9)	71.0 (29.7)	<0.001	73.6 (28.6)	0.331
80–89[a]	55.3 (31.8)	68.7 (30.9)	<0.001	74.1 (29.3)	0.109
>90[a]	62.5 (31.7)	66.3 (30.4)	0.893	79.2 (36.6)	0.172

[a]Indicates results reported as Geometric Mean (SD) quoted as nmol/L. The p-value for Bonferroni correction is 0.0013. Independent sample t-tests for continuous and cross tabulation with chi-squared and ANOVA for categorical were used. p-Value expressed with respect to initial test vs. first retest and first retest vs. ≥2 retests.

males and females. The increase in mean 25(OH)D on first retest was found in all age groups (p<0.001) except those >90 years. The 60–69 years group was the only one with a statistically significant improvement in mean 25(OH)D with ≥2 retests (p=0.002). Deficiency was halved on first retest (9 vs. 18%, p<0.001) dropping to 6% on further retests. Insufficiency also declined with each retest, irrespective of gender (p<0.013). Similarly, deficiency decreased between initial and first retest, and first and ≥2 retests in most age groups (Figure 1). There was a substantial decrease in deficiency between 1st and 2nd retest, regardless of season or location (see Figures 2 and 3). Excess vitamin D (>125 nmol/) were more prevalent (occurring in up to 4–5%) on retesting in both genders (p<0.001).



n D deficiency (<30 nmol/L) on retest by age category.
*Indicates significance (p<0.05).

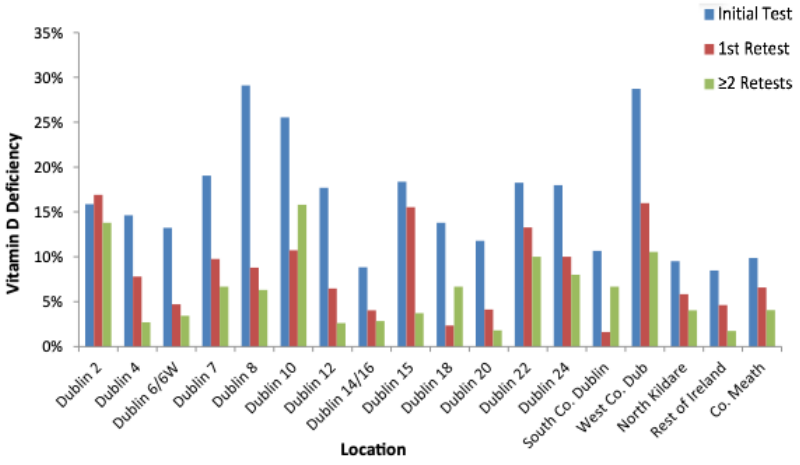


Figure 2: Summer rates of vitamin D deficiency by location.

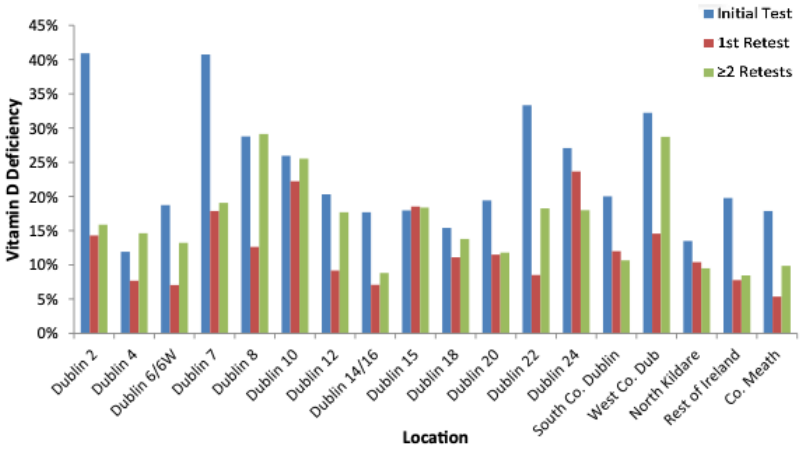


Figure 3: Winter rates of vitamin D deficiency by location.

Time to retest

About 12.2% of retests were completed within 3 months, as were 13.4% of ≥2 retests (Figure 4). The greatest number of first retests (17.2%) and subsequent tests (27.0%) were between 4 and 6 months. More than half of 1st retests (55.7%) and nearly three quarters (73.4%) of ≥2 retests took place within 12 months. However, a significant proportion of first retests (44.3%) and second retests (26.6%) occurred over 1 year later, though were not included as part of the

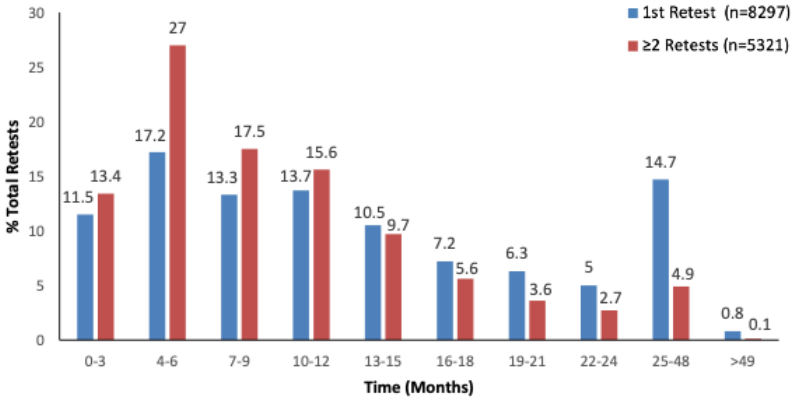


Figure 4: Time difference between vitamin D retests.
Time to ≥2 retests includes the time between the 2nd or later retests and the closest previous retest.

definition of inappropriate testing. Predictors of retest within 3 months of an initial test were younger age (55.2 years ± 17.4 vs. 55.9 years ± 16.2, p<0.001) but there was no difference in baseline 25(OH)D (71.4 ± 33.0 nmol/L vs. 69.9 ± 30.8 nmol/L, p=0.452) or female gender (74.6 vs. 72.1%, p=0.058).

Cost analysis

The NNT to identify one person with deficiency, insufficiency and levels >125 nmol/L at different testing points is shown in Table 4. The NNT to detect deficiency increased with the number of tests, ranging from six on initial testing to 17 on retesting. The NNT to detect excess vitamin D (>125 nmol/L) varied from 20 to 33. The NNT for deficiency was highest in 60–79 years and lowest in 18–39 years. NNT to detect deficiency varied by area across testing points.

Assuming €40 per vitamin D test, the cost of identifying one case of deficiency on initial testing ranged from €120 in those aged 18–39 years to €400 in those aged 60–79. On subsequent testing this rose to €1,000 or more. Retesting costs within 3 months of an initial test was €66,560. Furthermore, 29% of retests comprised a second or later retest within 12 months costing €156,240. Additionally, 26% of first retests were in those with an initial 25(OH)D level between 50 and 74 nmol/L costing €87,080. The total expenditure of inappropriate testing was €309,880 or €61,976 per year.

Table 4: Cost analysis of 25(OH)D testing.

	Initial test NNT	1st Retest NNT	≥2 Retests NNT	Initial test €	1st Retest €	≥2 Retests €
25(OH)D, nmol/L						
<30	6	11	17	240	440	680
30–50	4	5	6	160	200	240
>125	33	25	20	1,330	1,000	800
Gender (<30 nmol/L)						
Female	6	13	20	240	500	800
Male	5	10	17	200	400	600
Age, years (<30 nmol/L)						
18–39	3	6	7	120	240	280
40–49	5	8	11	200	320	800
50–59	7	13	20	280	520	800
60–69	10	25	33	400	1,000	1,320
70–79	10	25	33	400	1,000	1,320
80–89	6	17	25	240	680	1,000
<90	7	7	33	280	280	1,320
Location (<30 nmol/L)						
North Co. Dublin	4	8	13	160	320	520
South Co. Dublin	6	14	20	240	640	800
West Co. Dublin	4	7	10	160	280	400
Co. Kildare	9	13	25	360	520	1,000
Rest of Ireland	6	25	17	240	1,000	680

NNT was calculated by dividing the percentage with deficiency, insufficiency or 25(OH)D >125 nmol/L into 100 in each category (age, gender, location and retest point). The cost was calculated by multiplying the NNT by €40. NNT, number needed to test.

Discussion

Vitamin D retesting is common with one in four adults getting retested by their GP. Over 12% occurred within 3 months and a third represented ≥2 retests within the previous year. Those with vitamin D deficiency or insufficiency, female and aged 60–69 were more likely to get retested. Moreover, living in certain locations predicted greater likelihood of retesting. Over half (57%) of first retests were in vitamin D replete individuals, the majority of which may be considered inappropriate. As found elsewhere, vitamin D retests constituted a significant proportion of all requests [14, 30]. This may be due to increased patient led demand following greater public awareness of vitamin D with increased media reports of possible but yet unproven health benefits [13, 14, 30]. Despite the high number of vitamin D tests, there was no rise in retests over the 5 year study period.

Factors associated with retesting

Females constituted the majority of tests as reflected in other studies [24, 30, 31], despite having a lower rate of deficiency and insufficiency. More females experience osteoporosis, an indication for testing, but have higher rates of GP attendance and health seeking behaviour compared to males [32, 33]. As discovered elsewhere, those with initial vitamin D deficiency or insufficiency are more likely to have recurrent testing, explained by the need to assess supplementation efficacy and compliance [18, 34]. Age was a predictor of retesting, with those aged 18–39 least likely to be retested and most likely to be deficient, as previously found [14]. In retested patients, we found an improvement in vitamin D status in nearly all age

categories between initial and first retest, with a mean increase in 25(OH)D of 11 nmol/L. This increase is modest given a rise of up to 5.0 nmol/L per 100 IU of vitamin D supplemented may be expected [35]. Importantly, the overall prevalence of deficiency was halved on first retest (9%), dropping to 6% on further retests.

Over half (57%) who were retested were vitamin replete. The reasons for this are unclear though some guidelines suggest aiming for a vitamin D level of 75 nmol/L [20]. While vitamin D deficiency fell considerably between initial and repeat tests, nearly one in four (23%) still remained deplete after two or more retests. Factors such as poor compliance with supplements and inappropriately early retesting may account for this [36]. Additionally GPs may reassess vitamin D status based on seasonality or monitor for excess vitamin D [30]. Serum 25(OH)D typically drops by 10–20 nmol/L between late summer and winter, and so this must be factored in when interpreting results and the need to retest. Indeed, 3% had a levels above 125 nmol/L in our study and testing has also been found to be nearly four times higher in those on supplements [31].

Location was a predictor of retesting independent of age and initial vitamin D status, suggesting different reasons for GP requests by area. Patient led requests may account for some retesting and may be more likely in higher socioeconomic areas which are associated with greater health seeking behaviours such as GP attendance [37]. In Switzerland, those with a higher level of health insurance and living in urban areas were more likely to get tested [31]. In Ireland, 43% of the population have medical cards providing access to free GP care, which might influence patient led demand for vitamin D testing [38]. Patient reassurance has been identified as strong motivation for GPs to perform diagnostic tests [25]. In particular, maintaining a good relationship, avoiding conflict and creating good will for future consultations has been cited with regard to vitamin D testing [25]. A 'test me and treat me' patient perspective has also been noted in one study towards vitamin D testing and supplementation, with a focus on vitamin D in strongly medicalised terms [39]. It has been suggested that increased lay interest from science publications in the media, medicalisation of vitamin D and clinical uncertainty around testing may have fuelled recent the rise in tests [13, 39].

Inappropriate retesting and cost

We found 12% of retests were completed within 3 months and two or more retests were done within 1 year in nearly a third of cases. Similar retesting rates within short periods have been previously reported, with 20% of retests occurring within 3 months [30] and 38% taking place within 6 months [14]. In Canada, 40% of vitamin tests were inappropriate, defined as a retest within 3 months or more than two tests within 1 year [40]. Retests within 3 months may be considered redundant as it does not allow sufficient time for therapeutic correction of vitamin D deficiency [30, 41]. The significant level of early and repeat retesting is likely due to a lack of awareness of guidelines, though these are limited with most focussing on indications for initial testing. In addition, our laboratory like most in Ireland does not have a system in place at the point of ordering serum 25(OH)D that could help to eliminate inappropriate requests.

Annual expenditure on inappropriate vitamin D testing was €61,976 comprising those retested within 3 months, those retested who had initially levels between 50 and 74 nmol/L or two or more retests in the same year. There were large variances in the NNT to detect deficiency across population demographics and locations. Testing the youngest adults (18–39 years) was the most cost effective with €120 spent for every case of deficiency identified, increasing to €400 in those aged 60–79 and over €1,000 on retesting. Even at a cost of £12–20 per vitamin D test in the UK, the sheer volume of tests can result in substantial expenditure, placing pressure on the health service [13, 14].

Strategies to reduce inappropriate vitamin D testing

Excess vitamin D testing and rising costs have been highlighted in many countries, with different strategies employed to curb this. The solutions fall into two categories: (1) computer-based interventions at the point of ordering to reduce the number of inappropriate and unnecessary tests and (2) population based approaches, via supplementation or fortification, to eliminate deficiency and reduce the need for 25(OH)D monitoring.

Computer mediated interventions include two approaches. The first is a 'soft' stop where a pop-up reminder of criteria for vitamin D testing indications are presented, with an alert if there is no corresponding match of patient records to clinical guidelines [42, 43]. The second is a 'hard approach', where the test is limited to specific conditions [17, 18, 44, 45], certain medical specialities [43] or requesting algorithms, limiting repeat tests within specific time periods [46]. These strategies using different criteria have been utilised with varying levels of success and have resulted in reductions in vitamin D testing in the US [42], Denmark [18], Canada [44] and Italy [46]. In particular in

Alberta, Canada, there was a 92% reduction in testing while still including all relevant clinical indications [44]. However, in Australia the introduction of new testing criteria in 2014 resulted in an initial drop in requests, it was followed by an 8–13% increase in all age groups between 2016 and 2019 [47]. Different clinical indications between countries may partially explain the variation. For example, the guidelines are broader in some countries such as the US and Denmark [18, 42] and more restrictive in others including France and Canada [16, 44].

Another solution suggested by the Endocrine Society is population supplementation to decrease vitamin D deficiency and reduce the need for testing [20]. This may be considered an option as it remains unclear whether increased testing results in improved vitamin D status at a population level [13]. Alternatively, food fortification is another strategy. In Finland, after fortification of fat spreads and milk products, 91% of the population are now vitamin D sufficient (>50 nmol/L) though studies on its effect on testing are lacking [48]. In a modelling study of vitamin D deficiency in England and Wales, the estimated saving from fortification of wheat flour far outweighed the healthcare costs of preventing vitamin D deficiency, even without considering the economic burden of vitamin D testing [49]. However, genetic disorders such as 24-hydroxylase deficiency which increase the risk of vitamin D toxicity and hypercalcaemia need to be factored in when considering widespread fortification. Of note, supplementation of at-risk adults without prior vitamin D testing has been advocated during the current pandemic, given the potential benefits of vitamin D on either preventing COVID or reducing its severity [50].

In summary, given increasing vitamin D requests and high proportion of retests, strategies to promote appropriate testing would be helpful to curb mounting costs. Retesting should be considered where compliance with supplements is in question, malabsorption is suspected or in conditions such as osteomalacia/osteoporosis and hyperparathyroidism [21]. Retesting should generally not occur within 3 months. Based on our study, it is evident clear guidelines for GPs on vitamin D retesting is needed. As previous research suggests this action alone will not suffice in reducing inappropriate requests [18] and should be coupled with interventions at the point of ordering vitamin D. However, in order to improve patients status and reduce laboratory costs this needs to be combined with appropriate treatment. In Ireland, the HSE has recommended that a user-friendly GP ordering system for vitamin D is developed in GP information systems [28]. However, this has yet to be implemented. In the future, other assessments of 25(OH)D that better gauge status over a longer time period might provide a better alternative to retesting such as hair measurements [51].

Strengths

This is the largest study to investigate vitamin D retesting in Ireland. Vitamin D was measured using the gold standard method of LC/MS with strict adherence to quality control measures. We included a large dataset collected over a 5 year period with data on geographical areas of testing, with vitamin D status across several time points. We also did cost evaluations for detecting deficiency within population demographics.

Limitations

We did not have information on the indications for vitamin D testing or retesting nor any data on patient medical history, medications or supplement use, biophysical factors or sun exposure. We could not identify those who may have been tested before or after the study period meaning a proportion of patients may have been incorrectly categorised as non-retested.

Conclusions

Vitamin D testing is frequent with one in four adults getting retested by their GPs. Furthermore, 12.2% of all retests were done inappropriately early (within 3 months), a third too frequently and over half in initially vitamin D replete patients (>50 nmol/L). Differences in retesting by age, gender and location emphasize the need for clear national guidance for GPs on vitamin D testing laboratory ordering systems that limit requests based on pre-defined criteria should be considered. Population based strategies to reduce vitamin D deficiency may be more effective than the current practise of testing.

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Chapter 5: Low Socioeconomic Status Predicts Vitamin D Status in a Cross-Section of Irish Children

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RESEARCH ARTICLE

Low socioeconomic status predicts vitamin D status in a cross-section of Irish children

Helena Scully[1,2]*, Eamon Laird[2], Martin Healy[3], Vivion Crowley[3], James Bernard Walsh[1] and Kevin McCarroll[1]

[1]*Mercers Institute for Research on Ageing, St James's Hospital, Dublin 8, Ireland*
[2]*School of Medicine, Trinity College Dublin, Dublin 2, Ireland*
[3]*Department of Biochemistry, St James's Hospital, Dublin 8, Ireland*

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Abstract

Vitamin D is essential for bone and muscle health with adequate status in childhood crucial for normal skeletal development. We aimed to investigate vitamin D status in a convenience sample ($n = 1226$) of Irish children (aged 1–17 years) who had serum 25-hydroxyvitamin D (25(OH)D) tested by request of their GP at a Dublin Hospital between 2014 and 2020. We examined predictors including age, sex, season and socioeconomic status (SES). Vitamin D deficiency (<30 nmol/l) was prevalent affecting 23 % and was more common in disadvantaged areas (34 %) and in those aged >12 *v.* ≤12 years (24 % *v.* 16 %, $P = 0{\cdot}033$). The greatest predictor was SES (disadvantaged *v.* affluent, OR 2·18, CI 1·34, 3·53, $P = 0{\cdot}002$), followed by female sex (OR 1·57, CI 1·15, 2·14, $P = 0{\cdot}005$) and winter season (October to February, OR 1·40, CI 1·07, 1·84, $P = 0{\cdot}015$). A quarter of our sample of children were deficient, rising to one-third in those in disadvantaged areas. Females and those aged over 12 years had a higher prevalence of deficiency. Public health strategies to improve vitamin D status in Irish children, including systematic food fortification may need to be considered to address this issue.

Key words: 25(OH)D: Childhood: Ireland: Socioeconomic status: Vitamin D: Vitamin D deficiency

Introduction

Vitamin D (cholecalciferol) is a secosteroid produced via the action of Ultraviolet-B (UVB) light on skin. It is essential for the adequate absorption of calcium from the gastrointestinal tract and normal skeletal development[1]. Vitamin D deficiency (25 hydroxyvitamin D (25(OH)D) <30 nmol/l) in children can lead to impaired bone mineralisation causing rickets or osteomalacia[1]. Concernedly, a case study of Irish infants in 2006 suggests a rise in rickets incidence[2], as found in the UK, where cases have reached a 50-year peak[3]. While the overall prevalence of rickets is low, those at increased risk include young children under 5 particularly those of Black and South-east Asian ethnicity[4].

Importantly, peak bone mass in adolescence and early adulthood is influenced by vitamin D status and may account for 60 % of osteoporosis risk in later life[5]. Vitamin D may also have a role developmentally in early life consistent with the Barker fetal origins hypothesis[6]. For example, it may be important in fetal epigenetic programming of respiratory conditions in childhood[7] and has been associated with language and motor skill development, and risk of autism and ADHD[8,9]. Deficiency in childhood has been associated in some studies with extra-skeletal diseases[9] such as hypertension[10], diabetes[11,12], depression[13], dental caries[14], atopy and asthma[15,16]. Additionally, vitamin D might support childhood immune function with evidence suggesting a protective effect against respiratory tract infections. However, randomised control trials are required to further explore these associations[17].

Due to Irelands' north latitude (53°N), little or no vitamin D can be synthesised during winter months and adult deficiency

* **Corresponding author:** Helena Scully, email scullyhe@tcd.ie

is prevalent[18,19]. However, studies in Irish children and adolescents are limited, with deficiency (<30 nmol/l) ranging between 5 and 22 % and levels <50 nmol/l reported to be between 27 and 89 %[20–23]. Factors related to familial socioeconomic status (SES) have been suggested to affect vitamin D including lower diet quality, reduced intake of oily fish and supplement intakes and less access to outdoor amenities[24–26]. While some studies in Ireland have looked at the predictors of vitamin D, none have investigated any relationship with SES in children. In the UK, social deprivation and lower household income has been found to be independently associated with childhood vitamin D deficiency[27,28].

Given the limited studies in Ireland, we aimed to assess the association of SES and vitamin D status in children (1–17 years) in the Dublin area and surrounds who had 25(OH)D levels tested at our hospital laboratory by request of their General Practitioner (GP). In addition, we aimed to identify the prevalence of deficiency and its variation by age, sex and season. We also examined the proportion of children who were retested and factors associated with this.

Methods

Data collection

Data were collected at St James's Hospital (SJH), Dublin, Republic of Ireland (53° Northern Latitude). It serves a population of approximately 350 000 and receives referrals primarily from Dublin city and its surrounds. Using the laboratory information system (iSOFT Telepath®) at SJH Biochemistry Department, a search was completed for vitamin D requests from primary care GPs between 2014 and 2020. A convenient sample was identified using the following exclusion criteria: age ≥18 years on initial test, incomplete or missing demographic data, non-community address (e.g. Hospital) or location outside the Republic of Ireland. We also identified any repeat vitamin D tests (i.e. retests) for each participant during the study period.

Socioeconomic status

Participant socioeconomic status (SES) was assessed by mapping postal addresses using the 2016 Pobal HP (Haase-Pratschke) Deprivation Index[29]. This is a composite score of demographic profile, social class composition and labour market situation of small areas based on the 2016 Census of the Population. Small areas (100 households mean) are given a Relative Index Score that is then categorised into the following groups: extremely disadvantaged (≤−30), very disadvantaged (−20 to −29·99), disadvantaged (−10 to −19·99), marginally below average (0 to −9·99), marginally above average (0–9·99), affluent (10–19·99), very affluent (20–29·99) and extremely affluent (≥30). In this analysis, categories were combined into four groups: (1) disadvantaged (extremely disadvantaged, very disadvantaged, disadvantaged), (2) below average, (3) above average and (4) affluent (extremely affluent, very affluent, affluent), as previously described[30].

Ethics

Ethical approval for this study was granted by the St James's Hospital/Tallaght University Hospital (SJH/TUH) joint ethics committee (Ref: 5475). This study was conducted according to the Declaration of Helsinki 1964 guidelines.

Serum 25(OH)D and biochemical markers

Vitamin D (total 25(OH)D2 and 25(OH)D3) was measured using liquid chromatography tandem mass spectrometry (LC-MS/MS) (API 400; AB SCIEX) at the Biochemistry Department of SJH. A validated method (Chromsystems Instruments and Chemicals GmbH; MassChrom 25-OH-Vitamin D3/D2) accredited to ISO 15189:2012 standards was employed for analysis. Assay quality was ensured by participation in the vitamin D External Quality Assessment Scheme (DEQAS) and assay of internal and third-party quality controls and has been accredited by the Irish National Accreditation Board (INAB). Our vitamin D results fall within 3·5 % of the target control value, and this was similar for all years during the study. Accuracy was determined using the National Institute of Standards and Technology (NIST) 972 25(OH)D standard reference material (SRM 972). The respective inter- and intra-assay coefficients of variation are 5·7 and 4·5 %. In this study, we defined deficiency: <30 nmol/l, insufficiency: 30·0–49·9 nmol/l and sufficiency: ≥50 nmol/l[31]. Participants with 25(OH)D level >125 nmol/l were also identified as there may be associated health risks above this concentration[31]. Winter was defined as (October–February); and summer (March–September) as used elsewhere[32].

Statistics

Statistical analysis was carried out using SPSS (Version 26, IBM Corp., Armonk, NY, USA). The population was dichotomised by age (≤12 or >12 years) as in previous studies[33–35]. Data were checked for normality by the Kolmogorov–Smirnov test. Geometric mean with standard deviation was reported in tables. Categorical variables were tested using χ^2, with independent sample *t*-tests, one-way ANOVA and Kruskal–Wallis test for continuous variables. Statistical significance was accepted when $P < 0{\cdot}05$. Independent factors associated with vitamin D deficiency were explored in multi-nominal logistic regression models using the following variables: age category, sex, socioeconomic status and season of sampling. In a similar model, we explored for predictors of vitamin D retesting.

Results

Demographics of the cohort are shown in Table 1. Vitamin D results (not including retests) were initially identified for 1294 children aged between 1 and 17 years. After exclusion of participants with no available address ($n = 25$), and in whom SES could not be mapped ($n = 43$) the final number was 1226. The majority (69·2 %) were female and 89·3 % were aged >12 years. A similar proportion was tested in summer (56·5 %) and winter (43·5 %). The most prevalent SES classification was above average (43·6 %), followed by affluent (37·5 %), below average (11·1 %) and disadvantaged (7·8 %). The number tested was lower in 2014/2015 with annual increases

Table 1. Population demographics

Category		*n*	%
Age	≤12 years	131	10·7
	>12 years	1095	89·3
SES	Affluent	460	37·5
	Above Average	534	43·6
	Below Average	136	11·1
	Disadvantaged	96	7·8
Season	Winter	533	43·5
	Summer	693	56·5
Sex	Female	848	69·2
	Male	378	30·8
Year	2014	74	6·0
	2015	103	8·4
	2016	191	15·6
	2017	188	15·3
	2018	214	17·5
	2019	241	19·7
	2020	215	17·5
Total		1226	

thereafter in the period up to 2019. Nearly one-fifth (17·6 %, *n* = 228) of participants had vitamin D retested in the study period.

Overall, 23 % were vitamin D deficient, ranging from 20·1 % in summer to 25·9 % in winter (Table 2). More than half (50·6 %) had levels below 50 nmol/l, which was more common in winter compared to summer (55·3 % *v.* 46·9 %, *P* = 0·003). Mean 25(OH)D was higher in those aged under *v.* older 12 years (43·3 nmol/l *v.* 49·5 nmol/l, *P* = 0·020). It was also lower in females *v.* males (42·3 nmol/l *v.* 47·6 nmol/l, *P* = 0·008) but the difference was only significant in winter (39·4 nmol/l *v.* 45·7 nmol/l, *P* = 0·021). Serum 25(OH)D also varied by year ranging from an average of 39·1 nmol/l in 2018 to 50·7 nmol/l in 2014 (*P* < 0·001).

Females had a higher prevalence of deficiency *v.* males (25 % *v.* 17 %, *P* = 0·003) but this remained significant only in winter (29 % *v.* 18 %, *P* = 0·006) (Fig. 1). There was also a lower proportion of females *v.* males who were vitamin D sufficient (≥50 nmol/l) in both seasons but this was not statistically significant. The overall prevalence of 25(OHD) >125 nmol/l was 0·6 % with no difference by season or sex.

Vitamin D deficiency was more prevalent in those aged over *v.* under 12 years (23 % *v.* 15 %, *P* = 0·034). In the over 12s, deficiency was also greater in winter *v.* summer (27 % *v.* 21 %, *P* = 0·021) (Fig. 2). Those aged over 12 years had more sufficiency in summer *v.* winter (53 % *v.* 43 %, *P* = 0·002). We also found more deficiency in those ≤12 years in summer *v.* winter but this was not statistically significant. The prevalence of serum 25(OH)D >125 nmol/l was 0·7 and 0·5 % in the under and over 12s. Overall, levels of deficiency were significantly higher (26 % *v.* 20 %, *P* = 0·015), and sufficiency significantly lower (45 % *v.* 53 %, *P* = 0·003), in winter *v.* summer.

Vitamin D status and concentration by socioeconomic category are presented in Table 3. The difference in vitamin D status was greatest between affluent and disadvantaged areas. Children in below or above average areas had intermediate vitamin D levels with little difference between both of these SES categories, though being higher than disadvantaged. There were also significant differences in deficiency by area (*P* = 0·0018) ranging from 34 % in disadvantaged to 20 % in affluent areas. Similarly, the lowest prevalence of levels below 50 nmol/l was identified in affluent compared to disadvantaged areas (46 % *v.* 61 %, *P* = 0·019) (Fig. 3). When comparing below and above average SES, there was no difference in the prevalence of deficiency (*P* = 0·866) or levels between 30 and 49 nmol/l (*P* = 0·312). There were no significant differences in serum 25(OH)D in females (*P* = 0·051) or males (*P* = 0·127) across SES categories but sample sizes were smaller. In both those over and under 12 years, there was a significant difference in vitamin D status (*P* < 0·05) by SES with higher levels in affluent areas. Summertime vitamin D status was also significantly different across SES categories (*P* = 0·010) and highest in affluent areas.

Predictors of vitamin D deficiency are shown in Table 4. The greatest predictor was living in a disadvantaged location (OR 2·18, CI 1·34, 3·53, *P* = 0·002), followed by female sex (OR 1·57, CI 1·15, 2·14, *P* = 0·005), and testing in the winter (OR 1·40, CI 1·07, 1·84, *P* = 0·015). Age was not an independent predictor, though the number under 12 years was small (*n* = 139) and the analysis was likely to be underpowered to detect a significant difference.

Predictors of vitamin D retesting are shown in Supplementary Table S1. Baseline deficiency was the greatest predictor (OR 1·77, CI 1·22, 2·56, *P* = 0·003), followed by insufficiency (OR 1·76, CI 1·24, 2·49, *P* = 0·002) and female sex (OR 1·45, CI 1·03, 2·03, *P* = 0·032). There was a trend for reduced testing in those living in disadvantaged (OR 0·55, CI 0·29, 1·05, *P* = 0·068) and above average locations (OR 0·72, CI 0·52, 1·00, *P* = 0·052).

Table 2. Serum 25(OH)D status and concentration by age and sex (dichotomised by season)

Category	*n*	Total	*P*-value	*n*	Winter	*P*-value	*n*	Summer	*P*-value
25(OH)D	1226	43·9 (25·3)		533	41·2 (24·4)		693	46·1 (25·7)	<0·001*
<30 nmol/l (%)	277	22·6		138	25·9		139	20·1	0·015*
<50 nmol/l (%)	620	50·6		295	55·3		325	46·9	0·003*
Sex									
Female	848	42·3 (25·3)	0·008	376	39·4 (24·8)	0·021	472	44·8 (25·5)	0·148
Male	378	47·6 (25·0)		157	45·7 (23·1)		221	49·0 (26·2)	
Age									
≤12 years	131	49·5 (25·4)	0·020	56	46·8 (21·3)	0·053	75	51·6 (27·9)	0·147
>12 years	1095	43·3 (25·2)		477	40·5 (24·7)		618	45·5 (25·4)	

25(OH)D reported as Geometric mean ± (standard deviation) in nmol/l.
* *P*-value for winter season (October–February) *v.* summer season (March–September). *P*-values are reported for within category differences, using Mann–Whitney *U* or χ^2 test.

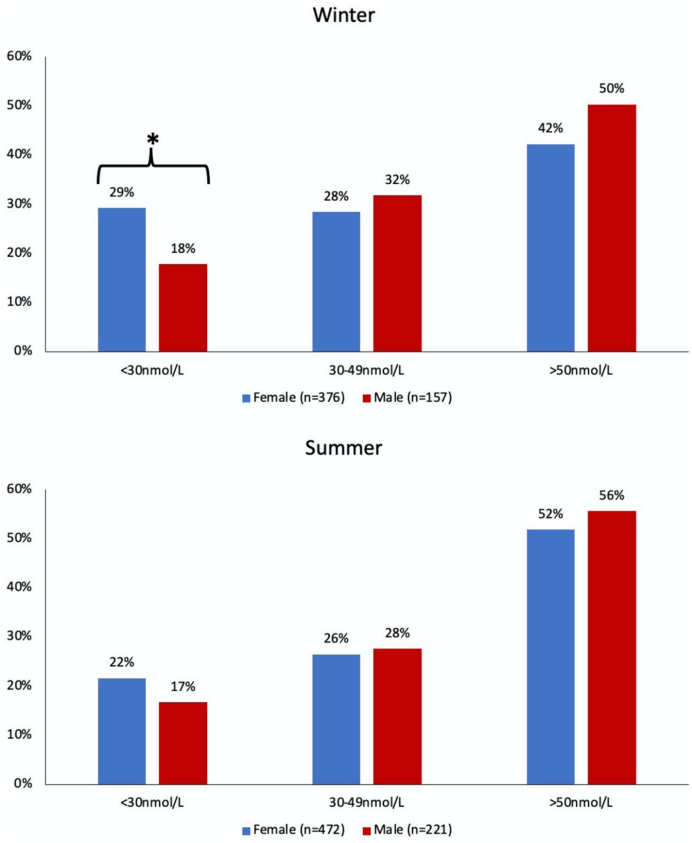

Fig. 1. Vitamin D status by sex. *Indicates significance ($P < 0{\cdot}05$) analysed by χ^2. Winter (October–February); Summer (March–September).

Discussion

This is the largest investigation of vitamin D status in a convenience sample of Irish children and adolescents and the only one to explore the association with SES. We identified that 23 % overall were vitamin D deficient (<30 nmol/l), rising to 34 % in children living in disadvantaged areas. In total, half of the cohort had concentrations less than 50 nmol/l, indicating that inadequate vitamin D status is highly prevalent. The greatest predictor for deficiency was living in disadvantaged locations, followed by female sex, and testing in the winter (October–February). Those over 12 also had lower vitamin D status than those under 12 years. We also showed that about one in five children were retested which is similar to that found in Irish adults[36], with predictors of retesting including initial deficiency/insufficiency and female sex.

Vitamin D status by socioeconomic status

Children living in disadvantaged areas were more than twice as likely to be vitamin D deficient compared to affluent children. This is the first study in Ireland examining the effect of SES on vitamin D status in children. The only other Irish study investigating vitamin D status and SES was in older adults as part of the TILDA study, which found that those with below average asset wealth had 1·5 times increased prevalence of vitamin D deficiency[19]. In the UK, low socioeconomic status has also been associated with greater deficiency[27,28] and similar results have been identified in the Netherlands[37], Greece[38] and Canada[39].

Lower SES may impact on vitamin D status as it has been associated with factors (e.g. reduced physical activity outdoors) that may lower UVB exposure[40], reduced dietary and supplemental vitamin D intake and greater obesity prevalence[24–26]. Supplements are a key contributor of vitamin D intake in Irish children and adolescents[41,42]. However, low supplement use has previously been found in children in low income or food insecure households[25] and has also been correlated with parental education[43]. Total vitamin D intake has been identified as being lower in children in lower income families in the UK and Spain[44,45]. This may be due to an increased

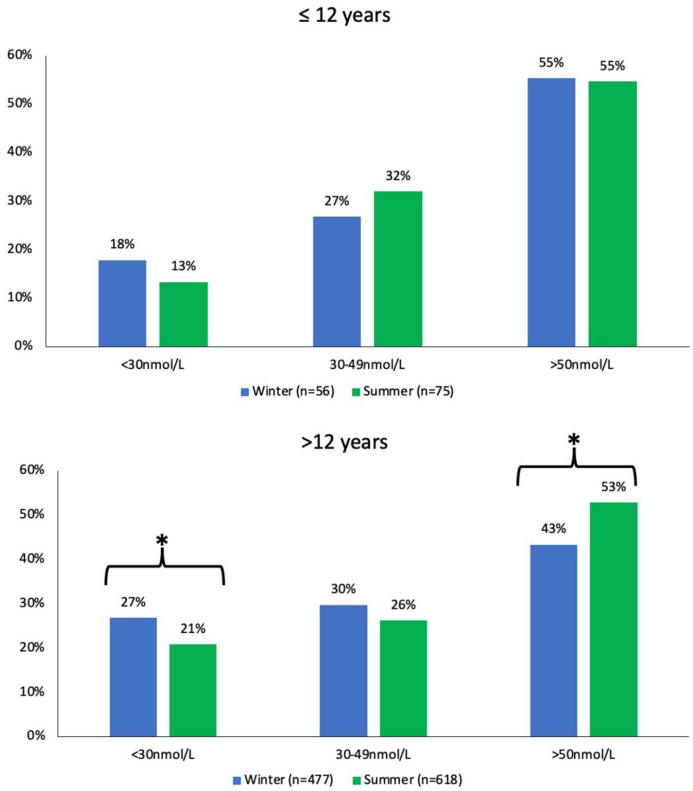

Fig. 2. Vitamin D status by age. *Indicates significance ($P < 0{\cdot}05$) analysed by χ^2. Winter (October–February); Summer (March–September).

prevalence of unhealthy eating in low SES children with lower consumption of vitamin D-rich foods including oily fish, meat and fortified food[24,46,47]. Furthermore, lower serum 25(OH) D has been found in Canadian children ($n = 1753$) from lower income families[48]. Studies of Irish adults have also found an association with disadvantaged backgrounds and a lower likelihood of meeting dietary vitamin D intake recommendations[49] with lower consumption of foods that are typical

Table 3. Serum concentration 25(OH)D by socioeconomic status category

		Socioeconomic status category				
nmol/l	*n*	Disadvantaged	Below average	Above average	Affluent	*P*-value
Overall	1226	38·1 (23·7)	43·0 (26·6)	43·1 (25·5)	46·5 (24·7)	0·005*
<30 (%)	227	34	24	23	20	0·018*
<50 (%)	343	61	49	53	46	0·019*
Sex						
Male	378	37·7 (24·2)	47·5 (25·1)	47·3 (26·0)	50·4 (23·8)	0·127
Female	848	38·2 (23·7)	41·3 (27·2)	41·4 (25·1)	44·8 (25·1)	0·051
Age (years)						
≤12	131	36·9 (14·9)	57·6 (19·6)	44·3 (27·4)	56·2 (24·0)	0·031*
>12	1095	38·1 (24·1)	41·2 (27·2)	42·9 (25·3)	45·5 (24·7)	0·020*
Season						
Winter	533	37·3 (21·5)	39·5 (27·9)	40·6 (24·6)	43·0 (23·7)	0·271
Summer	693	38·6 (25·3)	45·7 (25·6)	44·9 (26·0)	49·8 (25·2)	0·010*

25(OH)D reported as Geometric mean ±(standard deviation) in nmol/l. Winter (October–February); Summer (March–September). *P*-values are reported for within category differences, using χ^2 or Kruskal–Wallis test.
* Indicates significance at <0·05 level.

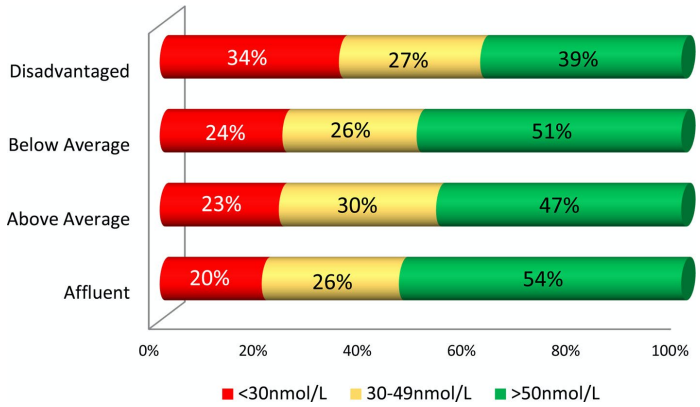

Fig. 3. Vitamin D status by socioeconomic status.

sources of vitamin D including fish, meat and breakfast cereals. In the US, vitamin D intake in children and adults was also correlated with income, with greater levels shown in the highest income group[50,51].

Another factor that may help explain vitamin D status by SES group is differences in rates of obesity. For example, obesity or overweight status in Irish children was more prevalent in those attending disadvantaged schools[52]. Obesity is associated with lower vitamin D in children, possibly due to its sequestration in adipose tissue[53]. We also identified seasonal differences in vitamin D status across SES categories, with those in affluent areas having higher serum levels in summer. This could be related to increased sun holiday travel, which is a reported determinant of vitamin D status in Irish adults[54]. Additionally, higher socioeconomic status is associated with reduced screen-time, increased access to outdoor activities and engagement in organised sports in adolescents, resulting in increased sun exposure[26,55,56]. In deprived areas, there may be reduced access to parks/playgrounds/gyms, which could also lower UVB exposure[56,57].

Vitamin D status by age

We identified that children aged >12 years had a greater prevalence of deficiency consistent with other studies in Europe, the US and Asia[27,58–60]. The only other Irish study comparing vitamin D status by age category was small ($n = 252$) and found a lower mean 25(OH)D in 12–17 years old *v.* those aged 1–4 years[20]. A larger Irish study of toddlers (aged 2 years) found a prevalence of deficiency (4·6 %) about five times lower than in the over 12s in our study[22]. Similarly, in the most recent UK National Diet and Nutrition Survey, deficiency was greater in those aged 11–18 (19 %) *v.* 4–10 years (2 %)[61]. In Europe, higher rates of deficiency (<30 nmol/l) were found in teenagers *v.* younger children[58]. Likewise, in a large US study ($n = 16\,180$), over 12s had the greatest prevalence of serum 25(OH)D (<50 nmol/l)[62]. Lower vitamin D status in older children may reflect reduced intake of vitamin D fortified foods, more sedentary behaviour or screen-time and higher rates of obesity[33,35,60]. Indeed, a dietary survey ($n = 594$) of Irish children and teens found a lower rate of supplement use and fortified foods in adolescents (13–17 years) *v.*

Table 4. Predictors of vitamin D deficiency (in multinomial regression)

Deficient (<30 nmol/l) *v.* non-deficient (≥30 nmol/l)	*n*	B	OR	Confidence Interval		*P*-value
				Lower	Upper	
Intercept	1226	−1·863				
Age ≤12 years	131	−0·47	0·625	0·379	1·032	0·066
Age >12 years†	1095					
Disadvantaged	96	0·778	2·176	1·34	3·534	0·002*
Below Average	136	0·256	1·292	0·814	2·052	0·277
Above Average	534	0·222	1·249	0·917	1·702	0·159
Affluent†	460					
Female	848	0·451	1·569	1·149	2·144	0·005*
Male†	378					
Winter	533	0·338	1·402	1·069	1·840	0·015*
Summer†	693					

B, unstandardised beta, OR, odds ratio.
* Indicates significance at <0·05 level.
† Indicates reference variable. Winter (October–February); Summer (March–September).

younger children (9–12 years)[41]. Increased vitamin D requirements in adolescence[63] due to an intensive period of new bone growth has also been proposed as a factor[31]. Finally, greater diagnosis of deficiency in older children might be in part due to more frequent presentation to GP's for chronic pain/medical symptoms or higher thresholds for vitamin D tests in younger children due to the challenges of phlebotomy[28].

Vitamin D status by season and sex

As expected, there was a seasonal variation in 25(OH)D, consistent with most studies[20,35,39,40], with more deficiency in winter *v.* summer. Furthermore, 55·5 % of children had a 25(OH)D below 50 nmol/l in winter. This figure is identical (55·3 %) to the recent finding in children ($n = 47$, age 7–11) living in Northern Ireland between November and March[21]. While the prevalence of deficiency/insufficiency varied by season in the under 12s, the difference was not significant, but is likely explained by the small sample size and lack of statistical power. A notable finding was the lower vitamin D status in females who were more likely to be deficient, a finding similar to other studies in Europe and elsewhere. For example, deficiency has been reported to be more common in Northern Irish female adolescents[64], female children in Britain[1,27], Greece[65] and the US[60]. Despite this, another study in Germany identified more deficiency in males[66].

We did find though that the difference in 25(OH)D status by sex was only significant in winter, albeit with a trend for better vitamin D status in males in summer. Dietary intake may be a contributory factor as female children have been found to have a lower vitamin D intake and consume less vitamin D fortified foods[67–69]. Body composition during puberty may play a role, with females acquiring greater fat mass during maturation[70]. Additionally, it is possible that adolescent girls may engage more in veganism, as found in female adults[71], which could lower vitamin D intake due to avoidance of meat and milks, that are significant sources of dietary vitamin D[35]. Females within ethnic minorities may also have reduced exposure due to religious dress[26]. On the other hand, male adolescents are reported to engage in more outdoor activity which affords more opportunity for sun exposure[27,64]. They are also less likely to use sunscreen or take measures to avoid sunburn[72] and may have more cutaneous exposure to summer UVB due to less clothing cover[27,73]. Finally, it has been suggested that higher overall GP consultation rates for girls than boys might account in part for a greater diagnosis of deficiency[28,74].

Guidelines on vitamin D intakes and implications

The Food Safety Authority of Ireland (FSAI) advise a vitamin D intake of 5 µg/d for children aged 1–5 years[2] though have only a blanket recommendation of 10 µg/d for those aged 5–65 years[75]. Guidelines are similar in the UK, with an intake (RNI) of 10 µg/d for those aged >4 years and a 'Safe intake' of 10 µg/d between 1 and 4 years[1]. However, the European Food Safety Authority (EFSA) and the US Institute of Medicine (IOM) recommend a higher dietary allowance of 15 µg/d between 1 and 18 years[75,76]. Despite more conservative guidelines in Ireland, 70–84 % of 1–4-year olds[34] and 94 % of 5–18-year olds have inadequate vitamin D intakes[33,35].

Indeed, it has been suggested that vitamin D intakes for children may need to be substantially higher. For example, an estimated total vitamin D intake (dietary and supplemental) of 33·8 µg/d may be required for 97·5 % of children living at 40–63°N to be vitamin D sufficient (>50 nmol/l) in the winter[77]. However, guidelines alone may not improve vitamin D status. In Canada, after dietary guidelines for vitamin D intake increased from 5 to 15 µg daily for those aged 1–70 years, an actual increase in vitamin D insufficiency (<50 nmol/l) was identified in those aged 6–18 years[78]. Targeted systematic vitamin D fortification of food is another option, as occurred in Finland in 2003. However, while it led to 91 % of over 30s in the population achieving 25(OH)D >50 nmol/l[79], it produced little improvement in vitamin D intake or serum levels in adolescent females[67] who had lower fortified food consumption[80]. The significant prevalence of vitamin D deficiency in our cohort of children suggests that vitamin D intakes are inadequate for a sizeable proportion of those aged 1–17 years, particularly in disadvantaged areas. Guidelines on vitamin D intakes that are specifically tailored to include all Irish children should be developed. However, as studies show these measures alone tend to be inadequate, other strategies including targeted vitamin D fortification of foods that are consumed by children needs to be considered.

Strengths

This is the largest study of vitamin D status in Irish children (1–17 years), and the first to investigate the association with socioeconomic status. We used a specific measure of SES, that is localised to a small area of 100 households, whereas most other studies used proxy measures such as parental education or household income. We used the gold standard of vitamin D measurement, LC-MS and adhere to strict quality monitoring (participation in DEQAS). We also utilised a dataset collected over a 7-year period that included and also explored for predictors of retesting.

Limitations

The present study is based on a convenient sample of GP vitamin D requests which limits the generalisability of the findings to a wider population. In particular, there may be selection bias of study participants who may have conditions predisposing to vitamin D deficiency that underlies the reason for their testing. We were not able to account for factors that influence serum 25(OH)D including biophysical (ethnicity, body mass index, medical conditions) or lifestyle (dietary/supplement intake, sun exposure or sunscreen use) due to the nature of the collected data. Finally, as the study is cross-sectional, we cannot infer any causality with regard to the factors we examined.

Conclusion

In conclusion, we identified that in a large convenience sample of children attending their GP in Ireland, those in the most

disadvantaged area had the highest level of deficiency, affecting 34 %. Furthermore, about one quarter of all children were found to be deficient. Childhood and adolescence are crucial periods for bone and muscle development, and deficiency may have long-term effects on both skeletal and other health outcomes. Targeted and tailored guidelines on vitamin D intake for all Irish children as well as public health promotion of its importance should be a priority. Development of a systematic policy of a vitamin D fortification of foods regularly consumed by children could be a realistic approach to help mitigate this issue.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/jns.2022.57.

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Chapter 6: Vitamin D: Determinants of Status, Indications for Testing and Knowledge in a Cross-Section of Irish Adults

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Vitamin D: determinants of status, indications for testing and knowledge in a convenience sample of Irish adults

Helena Scully[1,4]*, Eamon J. Laird[2,4], Martin Healy[3,4], Vivion Crowley[3], James Bernard Walsh[1,4] and Kevin McCarroll[1,4]

[1]*Trinity College Dublin School of Medicine, Dublin, Republic of Ireland*
[2]*Department of Sport and Exercise, University of Limerick, Limerick, Republic of Ireland*
[3]*Department of Biochemistry, St James's Hospital, Dublin, Republic of Ireland*
[4]*Mercer's Institute for Research on Ageing, St James's Hospital, Dublin, Republic of Ireland*

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Abstract

Vitamin D deficiency is common in Irish adults, though there is limited research on its determinants, knowledge of vitamin D or indications for testing. We aimed to explore the determinants of vitamin D status in adults and examine knowledge and reasons for testing. The study population comprised adults who had serum 25-hydroxyvitamin D tested by general practitioners request at a Dublin Hospital in 2020. Questionnaires detailing dietary intake, sun exposure, ethnicity, biophysical factors and vitamin D knowledge were sent to a sample stratified by age, sex and vitamin D status. In total, there were 383 participants, mean age 56·0 (SD 16·6) years. Wintertime deficiency disproportionally affected non-white *v.* white (60 % *v.* 24 %, $P < 0{\cdot}001$). The greatest predictors of deficiency were low vitamin D intake (< 10 μg/d) ($P < 0{\cdot}001$) and non-white ethnicity ($P = 0{\cdot}006$), followed by sun avoidance ($P = 0{\cdot}022$). It was also more prevalent in those with lower body exposure when outdoors. The majority (86 %) identified vitamin D as important for bone health. However, 40 % were tested for non-clinical indications and half were not aware of the recommended daily allowance (RDA). Low vitamin D intake was the most important determinant of deficiency, but ethnicity and sun exposure habits were also significant predictors. The majority had no clear indication for testing and were not aware of the RDA. Public health policies to improve knowledge and vitamin D intake, especially for those of non-white ethnicity and with reduced sun exposure, should be considered.

Keywords: **Vitamin D: Ireland: Determinants: Knowledge: Testing**

Vitamin D is primarily derived (80–90 %) from the action of UVB sunlight on dehydrocholesterol in the skin and apart from supplement use only a small proportion is obtained from dietary sources[1]. However, cutaneous synthesis is negligible between October and March in Ireland which results in a dependency on dietary vitamin D in winter months[2]. Apart from season, UVB exposure also depends on latitude, cloud cover, air pollution, sunscreen use and clothing while biophysical factors such as skin type and ageing can affect cutaneous synthesis[3,4]. However, the Irish diet is characteristically low in sources of vitamin D including cod liver oil and oily fish, with 87 % of men and 77 % of women not meeting the recommended intake (10 μg)[5,6]. Furthermore, only 10–17 % of Irish adults consume a supplement, yet this is the most consistent way of achieving adequate intake[5,7].

To date, most research on the determinants of vitamin D status in the Irish population has focused on older adults[7–10]. Overall, studies point to supplement use as the most important determinant[7,9,10]. Several have identified a characteristic seasonal variation and found positive associations with proxy measures of sun exposure (sun enjoyment, sun holiday travel, geographical UVB irradiation and sunshine hours)[4,10,11]. However, they did not specifically assess body skin exposure. Lower physical activity and frailty which may be indirectly linked to sun exposure have also been associated with lower vitamin D status[9,10]. Only four studies have investigated vitamin D status in a non-European ethnic demographic, finding lower 25-hydroxyvitamin D (25(OH)D) and a high prevalence of deficiency (< 30 nmol/l) between 57 and 88 %[12–15]. Few have examined the association with dietary or specific food intakes,

Abbreviations: RDA, recommended daily allowance; 25(OH)D, 25-hydroxyvitamin D.; FFQ, Food Frequency Questionnaire; Ca, Calcium.

* **Corresponding author:** Helena Scully, email helenascully@hotmail.com

though fortified milk, fish and egg consumption were found to be positive determinants in older adults and adolescents[4,10,16]. Biophysical factors such as increased BMI and female sex were also associated with lower vitamin D status in children and older Irish adults[7,9,16–18] while smoking, living alone and lower socio-economic status have been found to be negative predictors[9,10,19].

Despite an increase in referrals for vitamin D testing in Ireland and evidence of up to a third being done inappropriately (too early, too frequently or in replete individuals), no studies have explored the indications for these 25(OH)D assessments[20–22]. Furthermore, just one study investigated knowledge regarding vitamin D, but only in pregnant women where 70 % had little awareness of dietary sources[12]. Given the lack of studies, we aimed to explore in detail the biophysical, lifestyle and dietary determinants of vitamin D status in a diverse population of adults. Furthermore, we aimed to explore for the first time in Ireland indications for vitamin D testing, as well as adult knowledge of vitamin D.

Methods

Data collection

Data were collected at St James's Hospital (SJH), Dublin, Republic of Ireland (53° Northern latitude) which receives referrals primarily from Dublin city and surrounds. A search was completed for vitamin D requests from primary care general practitioners in 2020 using the laboratory information system (iSOFT Telepath®) at SJH Biochemistry Department. A convenience sample was identified using the exclusion criteria: age < 18 years, incomplete or missing demographic data, non-community address (e.g. hospital, nursing home, convent) or location outside the Republic of Ireland.

Participant screening and selection

Of the 13 669 results collected, 1639 were excluded due to incomplete data (*n* 423), age < 18 (*n* 262), non-community address (*n* 239) and repeat samples (*n* 715) (Fig. 1). This left a sample size of 12 030 from which we randomly selected 1260 adults initially stratified by season (winter: *n* 630, summer: *n* 630). Within each season, we further stratified by age (above 50 years, *n* 315, below 50 years, *n* 315) and then by vitamin D status (< 30 nmol/l, *n* 100; 30–49 nmol/l, *n* 100; 50–124 nmol/l, *n* 100 nmol/l; > 125 nmol/l, *n* 15). In this way, we were left with a sample of 1260 adults with an equal distribution of age, vitamin D status and season of testing to which questionnaires were sent. Participants were contacted via postal address with an information sheet, consent form and questionnaire which could be completed online (via link to survey monkey) or sent back manually in hard copy form in a pre-stamped, self-addressed envelope.

Questionnaire

The questionnaire we designed included thirty-three questions detailing medical information (indications for testing and pre-existing conditions that might affect vitamin D), biophysical (ethnicity, BMI, body size[23], socio-economic status (education level; third level or below), vitamin D intake (supplement and dietary intake) as well as dietary Ca intake using a FFQ, lifestyle (smoking, alcohol intake) and sun exposure (time spent in peak sunshine, sunscreen use, body exposure, sun-seeking habits). Information also included data on participants vitamin D knowledge (familiarity, awareness of health benefits and recommended daily allowance (RDA)). Questionnaires were sent to individuals between March and June 2022 and answers to our survey related to the period in which they had serum 25(OH) D tested. Reasons for vitamin D testing were queried, with routine health checks, patient requests and fatigue considered inappropriate.

Ethnicity was dichotomised into white and non-white (Black, Asian-Chinese, Asian-other and mixed). BMI category was determined based on self-identification using a 10 image scale of body sizes representing underweight, normal weight, overweight and obese as validated by Harris *et al.*[23]. We asked if participants had any of the following conditions that could affect vitamin D status (gastrointestinal conditions, e.g., Crohn's, coeliac disease, bowel/stomach surgery, inflammatory bowel disease), cystic fibrosis, liver/renal conditions, pancreatic disease and eating disorders.

Sun-seeking was categorised as no (avoid the sun) or yes (spend some time/seek the sun). Time spent outdoors was calculated based on the daily period spent outside between the hours of 13.00 and 17.00 during March to September. Body exposure was categorised as high, if more than face and hands exposed on a sunny day and otherwise as being low. Vitamin D familiarity was categorised as yes (extremely, very familiar) *v.* no (somewhat, not so, not at all familiar).

Vitamin D/Ca intake

Dietary vitamin D (μg) from food sources (unfortified and fortified) and Ca intake (mg) was calculated using a FFQ adapted from The Irish LongituDinal Study on Ageing questionnaire[9]. For each food consumed, an average vitamin D/Ca content per portion was estimated using food manufacturer's information and Nutritics software version 5.78 (online Supplementary Table 1). Where an approximate size of a food portion was not specified in the FFQ, an average portion size was assumed (e.g. yogurt = 125 g pot). In order to estimate daily dietary Ca and vitamin D intake, we initially calculated total weekly intake as follows: once per week (1 × unit food), 2–4 times per week (3 × unit food), 5–6 times per week (5·5 × unit food), once per day (7 × unit food), 2–3 times per day (2·5 × unit × 7) and 4–5 times per day (4·5 × unit × 7). The weekly total was then divided by 7 to give the total daily intake for vitamin D and Ca. We also dichotomised daily vitamin D intake from unfortified or fortified sources. The daily vitamin D intake from supplements (cod-liver oil, vitamin D only supplement, multivitamin containing vitamin D) was also calculated. Total daily vitamin D intake was then estimated by combining supplemental and dietary intake, and those who met the RDA were identified (10 μg/d as per advised by the Food Safety Authority of Ireland (FSAI) at the time of vitamin D sampling). We also identified those who exceeded the tolerable upper intake level for

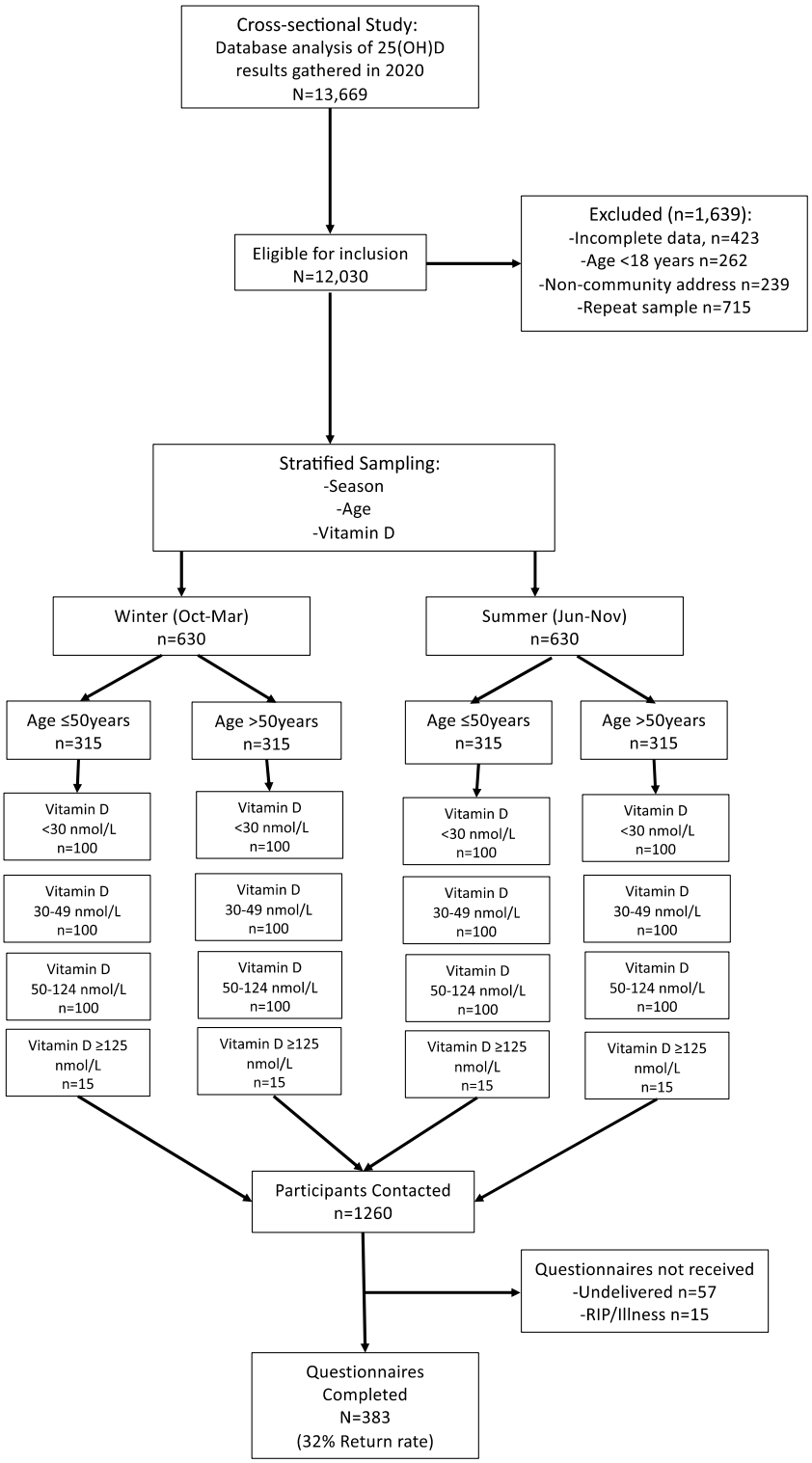

Fig. 1. Flow diagram.

vitamin D of 100 μg (4000 μg) per day[24] and who met the dietary Ca RDA (1000 mg/d in those aged 18–24 and 950 mg/d when aged > 25 years)[24].

Ethics

Ethical approval for this study was granted by the St James's Hospital/Tallaght University Hospital (SJH/TUH) joint ethics committee (Ref: 5658). This study was conducted according to the Declaration of Helsinki.

Serum 25-hydroxyvitamin D and biochemical markers

Liquid chromatography tandem mass spectrometry (API 400; AB SCIEX) was utilised to measure vitamin D (total 25(OH)D2 and 25(OH)D3) at the Biochemistry Department of SJH. A validated method of analysis was employed (Chromsystems Instruments and Chemicals GmbH; MassChrom 25-OH-Vitamin D3/D2) accredited to ISO 15189:2012 standards. Participation in the vitamin D External Quality Assessment Scheme and assay of internal and third-party quality controls ensured assay quality. National Institute of Standards and Technology 972 25(OH)D standard reference material (SRM 972) was used to determine accuracy. The inter- and intra-assay coefficients of variation are 5·7 and 4·5 %, respectively. Vitamin D cut-offs were defined according to the Institute of Medicine as deficiency: < 30 nmol/l, insufficiency: 30·0–49·9 nmol/l and sufficiency: ≥ 50 nmol/l[22,25]. Serum 25(OH)D ≥ 125 nmol/l was also identified as this level may constitute vitamin D excess and has been associated with some adverse health outcomes[25,26].

Statistics

Data were checked for normality by the Kolmogorov–Smirnov test. Geometric mean with standard deviation was reported in tables. Median and interquartile range were used to report dietary intakes. Categorical variables were tested using Chi-squared, with independent sample t-tests, Mann–Whitney and Kruskal–Wallis test for continuous variables. Independent factors associated with vitamin D deficiency (< 30 nmol/l) were explored in binary logistic regression models using the following variables and reference categories: age (≥ 50 years), sex (male), BMI category (normal weight), season of sampling (summer), ethnicity (white), smoking (non-smoker), alcohol (alcohol consumer), sun habits (sun seeker), education (third level) and adherence to vitamin D RDA (yes/no). Body exposure and hours spent in peak sunshine were co-correlated with sun-seeking behaviour and were therefore not included in the model. Statistical analysis was carried out using SPSS (Version 26, IBM Corp). Statistical significance was accepted when $P < 0{\cdot}05$.

Results

Demographics

Questionnaires were completed by 383 (32 %) of the contacted participants. In fifty-seven cases (4·5 %), they were not received by the participant due to a change of address, and in fifteen (1·1 %), they were not completed due to death or illness (Fig. 1). Characteristics of the sample are shown in Table 1.

Table 1. Population demographics (Numbers and percentages)

		n	%
Sex	Female	230	60
	Male	153	40
Age (years)	<50	145	38
	≥50	238	62
Age categories (years)	18–39	72	19
	40–49	69	18
	50–59	66	17
	60–69	87	23
	70–79	60	16
	>80	29	8
Season	Winter	219	57
	Summer	164	43
Condition affecting vit D*	Yes	79	21
	No	304	79
Ethnicity	White	344	90
	Non-white	39	10
BMI (*n* 380) (kg/m^2)	Underweight	26	7
	Normal weight	135	36
	Overweight/obese	219	58
Third level education (*n* 379)	Yes	256	68
	No	123	32
Smoking (*n* 379)	Yes	41	11
	No	338	89
Alcohol consumer	Yes	311	81
	No	72	19
Supplement user	Yes	192	50
	No	191	50
Sunscreen user (*n* 380)	Yes	271	71
	No	109	29
Sun seeker (*n* 380)	Yes	282	74
	No	98	26
Body exposure (*n* 380)	Low	73	19
	High	307	81
Time spent in peak sunshine (min)	0	74	19
	<30	64	17
	>30	245	64
Vitamin D familiarity	Yes	115	30
	No	268	70

Season: winter, Oct–Mar; summer, Apr–Nov. Conditions affecting vitamin D included gut/gastrointestinal diagnoses (e.g. Crohn's disease, coeliac disease, bowel/stomach surgery, inflammatory bowel disease), cystic fibrosis, liver/renal conditions, pancreatic disease and eating disorders. BMI was determined based on response to a 10-point image scale[23] on body size categorised as underweight, normal weight, overweight and obese. Sun-seeking was categorised as no (avoid the sun) or yes (spend some time/seek the sun). Body exposure was categorised as low if only face and hands or higher if additional body parts exposed on a sunny day. Time spent outdoors calculated based on the daily period spent outside between the hours of 13.00 and 17.00 during March to September. Vitamin D familiarity was defined as yes (extremely, very) *v.* no (somewhat, not so, not at all familiar).
*$P < 0{\cdot}05$.

The average age was 56·0 (SD 16·6) years, 60 % were female and 90 % were of white ethnicity. Two-thirds (67 %) had third level education and one-fifth (21 %) identified as having a condition that could predispose to lower vitamin D. The majority of the population were overweight or obese (58 %), with 36 % normal and 7 % underweight. Most participants were sun seekers (74 %), had a high UV body exposure (81 %) and used sunscreen (71 %) and were not familiar with vitamin D (70 %). About 50 % (192/383) were taking a vitamin D supplement with precise data on vitamin D content and dosing frequency available in 79 % (151/191). For this reason, the sample size (*n* 338) on which there was estimation of total vitamin D intake and analysis of RDA was smaller (Table 3). There was a near equal split between

Table 2. Vitamin D categories by season
(Numbers; mean values and standard deviations)

			GM			Winter							Summer						
		n	Mean	SD	*P*	*n*	<30 %	*P*	30–49 %	*P*	≥50 %	*P*	*n*	<30 %	*P*	30–49 %	*P*	≥50 %	*P*
Sex	Female	230	48·2	36·0	0·853	135	27	0·908	24	0·073	49	0·083	95	21	0·559	33	0·336	46	0·197
	Male	153	47·5	32·2		84	27		36		37		69	17		26		57	
Age	<50 years	145	48·5	38·3	0·704	81	30	0·492	26	0·477	44	0·974	64	20	0·836	22	0·703	58	0·140
	≥50 years	238	47·6	31·9		138	25		30		44		100	19		35		46	
Age category	18–39	72	43·3	39·1	0·380	40	40	0·129	25	0·335	35	0·113	32	22 %	0·979	25 %	0·372	53 %	0·528
(years)	40–49	69	54·0	37·1		37	22		24		54		32	19		19		63	
	50–59	66	47·3	31·4		43	26		42		33		23	17		26		57	
	60–69	87	50·9	32·9		51	16		27		57		36	19		36		44	
	70–79	60	44·0	34·2		34	35		21		44		26	23		35		42	
	>80	29	47·9	27·2		14	29		36		36		15	13		47		40	
Condition affecting vit D	Yes	79	47·1	35·1	0·774	37	38	0·101	22	0·292	41	0·614	42	19	0·930	36	0·338	45	0·419
	No	304	48·2	34·4		182	25		30		45		122	20		28		52	
Ethnicity	White	344	50·8	34·3	<0·001	199	24	<0·001	30	0·364	47	0·022	145	16	0·001	29	0·461	55	0·001
	Non-white	39	28·7	26·2		20	60		20		20		19	47		37		16	
BMI	Underweight	26	61·2	35·8	0·014	12	25	0·963	8	0·094	67	0·152	14	14	0·581	21	0·705	64	0·319
(*n* 380)	Normal Weight	135	51·2	41·5		83	28		24		48		52	15		29		56	
	Overweight/Obese	219	45·2	28·2		122	26		34		40		97	22		32		46	
Third level education	Yes	256	51·3	34·9	0·018	150	23	0·071	32	0·15	45	0·779	106	15	0·072	24	0·02	61	<0·001
(*n* 379)	No	123	42·6	33·1		67	34		22		43		56	27		41		32	
Smoking	Yes	41	40·0	33·8	0·065	23	43	0·047	35	0·521	22	0·019	18	33	0·104	17	0·201	50	0·912
(*n* 379)	No	338	49·5	34·5		194	24		28		47		144	17		31		51	
Alcohol consumer	Yes	311	51·3	34·2	<0·001	185	23	0·001	30	0·252	47	0·057	126	14	0·002	27	0·14	59	<0·001
	No	72	35·8	33·0		34	50		21		29		38	37		39		24	
Supplement user	Yes	192	60·0	37·0	<0·001	107	15	<0·001	21	0·009	64	<0·001	85	8	<0·001	28	0·634	64	0·001
	No	191	38·3	27·0		112	38		37		25		79	32		32		36	
Sunscreen user	Yes	271	52·5	36·0	<0·001	157	22	0·013	34	0·005	44	0·719	114	13	0·004	27	0·223	60	0·001
(*n* 380)	No	109	39·4	27·7		60	38		15		47		49	33		37		31	
Sun seeker	Yes	282	50·6	35·1	0·041	172	23	0·019	31	0·134	46	0·476	110	15	0·095	29	0·697	55	0·095
(*n* 380)	No	98	42·3	32·1		45	40		20		40		53	26		32		42	
Body exposure	Low	73	42·4	32·9	0·044	34	32	0·38	35	0·381	32	0·115	39	31	0·032	33	0·609	36	0·031
(*n* 380)	High	307	49·8	34·7		183	25		28		47		124	15		29		56	
Time spent in peak sunshine	0	74	44·8	34·3	0·531	41	37	0·225	20	0·131	44	0·840	33	24	0·745	36	0·186	39	0·118
(min)	<30	64	47·3	37·3		37	30		22		49		27	19		41		41	
	>30	245	49·1	33·9		141	23		33		43		104	18		25		57	
	Total	383	47·9	34·5		219	27		29		44		164	20		30		51	

GM mean, geometric mean; Vit D, vitamin D.
Vitamin D categories reported as % < 30 nmol/l, %30–49 nmol/l and % ≥ 50 nmol/l. Winter was defined as October–March, Summer: April–Sept. *P*-values were determined by Mann–Whitney or Kruskal–Wallis test for continuous variables, and Chi-squared was used for categorical, significant at $P < 0{\cdot}05$.

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Table 3. Predictors of vitamin D deficiency (< 30 nmol/l) in regression (Odds ratios)

Non-deficient (> 30 nmol/l) v. deficient (< 30 nmol/l)	*n*	B	OR	Lower, upper	*P*
Intercept		–3·099	0·045		
Age < 50	123	–0·284	0·753	0·379, 1·494	0·416
Female	204	0·173	1·189	0·661, 2·137	0·564
BMI – Underweight	22	–0·521	0·594	0·153, 2·308	0·452
BMI – Overweight/obese	194	0·045	1·046	0·571, 1·917	0·884
Ethnicity – Non-white	31	1·361	3·899	1·464, 10·379	0·006*
Smoking – Yes	36	0·655	1·924	0·817, 4·530	0·134
Alcohol – No	65	0·616	1·851	0·894, 3·831	0·097
Third level education – No	109	0·191	1·210	0·644, 2·275	0·553
Sun seeker – No	89	0·731	2·077	1·113, 3·876	0·022*
Meeting vitamin D RDA – No	189	1·267	0·282	0·15, 0·528	<0·001**

Logistic regression adjusts for all of the above variables and season. Reference category for each variable: meeting vitamin D RDA: yes; sun-seek: yes; third level education: yes; alcohol consumer: yes; smoking: no; ethnicity: white; BMI: normal weight; sex: male: age: ≥ 50 years.
*$P < 0·05$.
**$P < 0·001$

seasons, with 57 % of results in winter and 43 % in summer. In total, 24 % of this stratified convenience sample were vitamin D deficient (< 30 nmol/l), 29 % insufficient (30–50 nmol/l) and 5 % had levels > 125 nmol/l. The associations between vitamin D status and factors are discussed below and outlined in Tables 2 and 3.

Biophysical

There was no significant difference in 25(OH)D by sex or age (Table 2). However, those of white ethnicity had significantly higher mean 25(OH)D levels than non-white (50·8 *v.* 28·7 nmol/l, $P < 0·001$). They also had a substantially lower prevalence of deficiency (24 % *v.* 60 %, $P = 0·001$) and higher rate of sufficiency (47 % *v.* 20 %, $P = 0·022$) in winter. In summer, results for white *v.* non-white were also similar for deficiency (16 % *v.* 47 %, $P = 0·001$) and sufficiency (55 % *v.* 16 %, $P = 0·001$). Compared with the white population, the non-white cohort had a higher proportion < 50 years (77 % *v.* 33 %, $P < 0·001$) and of non-alcohol consumers (64 % *v.* 14 % $P < 0·001$), but there was no difference in supplement use, season of sample, smoking, education, body exposure or proportion meeting vitamin D RDA. Furthermore, being non-white was an independent predictor of deficiency (OR 3·90, 95 % CI 1·46, 10·38, $P = 0·006$) (Table 3). Vitamin D levels were also lower in those who were overweight or obese *v.* normal weight (45·2 *v.* 51·2 nmol/l, $P = 0·014$) but this was not found to be an independent predictor of deficiency. No significant difference in 25(OH)D was identified between those with or without a condition affecting vitamin D (47·1 *v.* 48·2 nmol/l, $P = 0·774$).

Lifestyle/social factors

There was a trend for a lower overall mean 25(OH)D concentrations in smokers *v.* non-smokers (40·0 *v.* 49·5 nmol/l, $P = 0·065$) though only in winter did they have a higher prevalence of deficiency (43 % *v.* 23 %, $P = 0·047$). Furthermore, smoking was not found to predict deficiency when adjusting for other factors. Alcohol users had higher 25(OH)D than non-users (51·3 *v.* 35·8 nmol/l, $P < 0·001$) and were also less likely to be deficient in winter (23 % *v.* 50 %, $P = 0·001$) and summer (14 % *v.* 37 %, $P = 0·002$). However, they were also more likely to be sun seekers (78 % *v.* 58 %, $P < 0·001$) and it was not identified as an independent predictor of deficiency (Table 3). Finally, those with third level education had higher 25(OH)D (51·3 *v.* 42·6 nmol/l, $P = 0·018$) and were more likely to have sufficient status in the summer (61 % *v.* 32 %, $P < 0·001$), but no relationship was found with deficiency in multivariable analysis.

Sun exposure

Sun seekers were more likely to have higher 25(OH)D (50·6 *v.* 42·3 nmol/l, $P = 0·041$) and lower prevalence of deficiency in winter (23 % *v.* 40 %, $P = 0·019$). Overall, those who avoided the sun were about twice as likely to be deficient (OR 2·08, 95 % CI 1·11, 3·88, $P = 0·022$) (Table 3). High body exposure was also associated with greater mean 25(OH)D (49·8 *v.* 42·4 nmol/l, $P = 0·044$) and less deficiency in summer (15 % *v.* 31 %, $P = 0·032$). There was no difference in mean 25(OH)D comparing those who spent more or less than 30 min in peak sunshine. Finally, sunscreen users had better 25(OH)D (52·5 *v.* 39·4 nmol/l, $P < 0·001$) and were less likely to be deficient in winter (22 % *v.* 38 %, $P = 0·013$) and summer (13 % *v.* 33 %, $P = 0·004$).

Dietary intakes

The overall contribution of diet to vitamin D intake was low with half of all participants consuming less than 4·5 μg (180 μg) per day. There was a trend for better vitamin D status with higher levels of vitamin D intake from either unfortified or fortified sources (Table 4). However, total dietary vitamin D intake (combining unfortified and fortified foods) was significantly lower in those who were deficient *v.* sufficient (4·0 *v.* 5·2 μg/d, $P = 0·044$). We also identified that those who were over 50 had higher dietary intakes (median 5·4 *v.* 3·7 μg/d, $P < 0·001$) and were more likely to consume oily fish on a weekly basis (60 % *v.* 30 %, $P < 0·001$). However, there was no difference in dietary intake by sex. We also found that the median dietary Ca intake was 658 mg/d and was significantly different by vitamin D status ($P = 0·004$): lowest in those with deficiency (527 mg/d) and highest with sufficiency (768 mg/d).

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Table 4. Vitamin D and Ca intake
(Medians and interquartile ranges)

		Total		< 30 nmol/l		30–49 nmol/l		≥50 nmol/l		
	n	Median	IQR	Median	IQR	Median	IQR	Median	IQR	*P*
Unfortified food	338	1·9	2·8	1·6	2·8	2·0	2·6	2·1	2·9	0·118
Fortified food	338	1·9	4·4	1·1	3·6	2·0	4·6	2·3	5·1	0·21
Unfortified and fortified	338	4·5	5·0	4·0	4·5	4·5	4·4	5·2	5·0	0·044
Supplement intake*	151	10·0	11·4	9·3	11·4	8·6	11·4	12·9	16·4	0·032
Total vitamin D intake	338	8·8	15·9	4·9	8·5	7·0	10·4	14·4	20·8	<0·001
Ca Intake	338	658·3	615·8	527·1	636·7	595·6	677·3	767·9	540·2	0·004

*Supplement intake dose (total cod-liver oil, vitamin D and multivitamin containing vitamin D) available for *n* 151. *P*-value determined by Kruskal–Wallis test, significant at $P < 0·05$. Values reported as median intake (interquartile range) in micrograms for vitamin D and milligrams for Ca.

Supplement intake

The median intake due to supplements was 10·0 µg (400 µg) per day. Higher supplement intake was identified in those who were sufficient *v.* deficient (median 12·9 *v.* 9·3 µg/d, $P = 0032$). Overall, those who took supplements had higher mean 25(OH)D (60·0 *v.* 38·3 nmol/l, $P < 0·001$) and were much less likely to be deficient in both summer (8 % *v.* 32 %, $P < 0·001$) and winter (15 % *v.* 38 %, $P < 0·001$). They were also more likely to be sufficient (64 % *v.* 30 %, $P < 0·001$). There was no difference in mean daily vitamin D daily intake from food in supplement users *v.* non-supplement users (6·9 *v.* 5·7 µg/d, $P = 0·251$). Supplement use was also not predicted by age, sex, season ethnicity or education when explored in binary logistic regression.

Total vitamin D intake and RDA

About half of participants had a total vitamin D intake (diet and supplements) of less than 8·8 µg (352 µg) per day, but fewer than 50 % of our study sample consumed a supplement. Median total intake was highest in those who were sufficient (14·4 µg/d) and lowest in deficiency (4·9 µg/d). In fact, total intake was twice as high in non-deficient *v.* deficient (11·1 *v.* 4·9 µg/d, $P < 0·001$), and nearly three times higher comparing sufficiency *v.* non-sufficiency (14·4 *v.* 5·8 µg/d, $P < 0·001$). Less than half the population (43 %) met the vitamin D RDA (online Supplementary Fig. 1). However, this was much more likely in supplement *v.* non-supplement users (81 % *v.* 13 %, $P < 0·001$). Furthermore, there was a substantially lower prevalence of deficiency (12 % *v.* 32 %, $P < 0·001$) and higher sufficiency (64 % *v.* 33 %, $P < 0·001$) in those meeting this RDA. Overall, those not achieving the RDA were 72 % more likely to be deficient (OR 0·28, 95 % CI 0·15, 0·53, $P < 0·001$) (Table 3). We identified that 30 % achieved the RDA for dietary Ca intake.

Vitamin D excess

Serum 25(OH)D levels ≥ 125 nmol/l were identified in nineteen respondents and were more likely in those aged <50 years ($P = 0·020$) and in supplement users ($P = 0·001$). The median total vitamin D intake in those with a level ≥ 125 nmol/l was 27·5 µg (1100 µg)/d) with the highest intake of 145 µg/d (5800 µg) in a patient with a serum concentration of 131 nmol/l. Overall, 1·5 % (*n* 5) had an intake above the tolerable upper intake level of 100 µg (4000 µg) per day[2] and the highest 25(OH)HD level identified in this group was 193 nmol/l.

Vitamin D knowledge and testing indications

The primary reason, in more than a third (34 %) of patients for testing, was for a routine health check. Appropriate reasons for testing included unexplained aches and pains (21 %), brittle bones (10 %) and limited sun exposure (9 %), though 19 % reported 'other' which included requests due to patient request (*n* 13), fatigue (*n* 7) and immunity/COVID (*n* 6) (online Supplementary Fig. 2). There was a lack of awareness of current vitamin D guidelines, with nearly half (46 %) not knowing, one-third (32 %) believing the RDA was more than 20 µg (1000 µg)/d and just 12 % correctly identifying 10–15 µg (400–600 µg)/d (online Supplementary Fig. 3). The vast majority (86 %) of respondents cited vitamin D as being important for bone health with 66 % citing immunity/COVID, 47 % heart health and 40 % mental health (online Supplementary Table 4). There was no difference in vitamin D status in those who were familiar *v.* not familiar with vitamin D (61·9 *v.* 55·5 nmol/l, $P = 0·097$). Vitamin D familiarity was predicted by education in binary logistic regression, with no effect found for age, sex, season or ethnicity. A total of 40 % (*n* 152) of referrals were inappropriate, including for routine health checks (*n* 132), patient request (*n* 13) and fatigue (*n* 7).

Discussion

This is the first study to investigate in detail the determinants of vitamin D status in Irish adults and to explore indications for testing as well as knowledge of vitamin D's role in health and its RDA. The strongest predicators for deficiency were low vitamin D intake (< 10 µg/d) and non-white ethnicity, and it was also twice as likely in sun avoiders. The contribution of dietary sources to overall intake was small, but it was still positively associated with better vitamin D status. However, the vast majority who met the RDA were taking supplements. More than a third had vitamin D testing for inappropriate reasons and less than 12 % could correctly identify the recommended dietary intake.

Vitamin D intake

The overall contribution of diet to vitamin D intake was low with half of all participants consuming less than 4·5 µg (180 µg) per day. The median intake due to supplements was 10·0 µg (400 µg) per day, and those taking supplements were about three

times less likely to be deficient in summer. The mean difference in serum 25(OH)D in users *v.* non-users of supplements was 21·7 nmol/l, which is similar to that found previously in older Irish adults and pregnant women[10,14,27]. Older adults had both higher dietary and total vitamin D intakes. These findings are in keeping with other dietary surveys in Ireland that found intakes between 3·0 and 6·9 μg/d, though being lower in younger (18–35 years) *v.* older adults (> 65 years)[6,28]. We found similar rates of supplement use by age in this study which contrasts to findings elsewhere[2,5]. However, oily fish consumption was more frequent in those > 50 in our survey which may partly explain their higher intake.

Nearly half (43 %) of adults did not meet the RDA for vitamin D while in those taking supplements this was lower at 19 %. However, some supplements, especially those over the counter, contain relatively small amounts of vitamin D and/or Ca. Importantly, those achieving the vitamin D RDA were 72 % less likely to be deficient though this still occurred in 12 % of our population. Previous meta-analysis studies estimated that 12–13 μg/d per day is required for the general population living ≥40°N to maintain wintertime vitamin D status ≥ 30 nmol/l[29,30]. However, previous dietary surveys in Ireland have found that just 10 % of adults meet the 10 μg/d level, indicating that fortification may be required to achieve adequate vitamin D intakes in the population[5,29]. In addition, 10 % of our survey participants were of non-white ethnicity, for whom studies suggest higher vitamin D intakes to optimise status[31]. Furthermore, the RDA (10 μg/d) on which we based our analysis was the recommendation at the time participants had their serum 25(OH)D tested. However, the FSAI more recently advised on a higher daily intake (15 μg/d) for older adults (aged >65) which constitute 32 % of our sample[32]. We found that 1·5 % of participants exceeded the tolerable upper intake level of 100 μg (4000 μg) per day, but the highest 25(OH)D level identified was below that which predisposes to acute vitamin D toxicity.

Ethnicity

Non-white ethnicity was associated with a very high prevalence of winter deficiency of 60 % *v.* only 24 % in white participants. Furthermore, 80 % of non-white ethnicity had levels <50 nmol/l in wintertime. The proportion in our survey who were non-white is also similar to that found in a recent census of the Dublin urban area[33]. There is very limited research on vitamin D status in ethnic populations in Ireland with only four studies published[12–15]. In South-East Asian adults (*n* 186) living in Dublin, 67 % had 25(OH)D < 30 nmol/l[13]. A high prevalence of deficiency (<30 nmol/l) was also identified in eighty-one pregnant women of Middle Eastern and African (88 %), Sub-Saharan (68 %) and Asian origin (59 %) *v.* Thirty-one indigenous Irish (36 %) living in Ireland[12]. A larger study of pregnant woman in Ireland found that those of non-white ethnicity had a mean 25(OH)D that was 19·3 nmol/l lower[14]. African ethnicity was also a significant determinant of vitamin D status in a small sample (*n* 7) of Irish children[15]. We found no difference in vitamin D intake, supplement use, education or body exposure between white and non-white participants suggesting that ethnic difference in skin pigmentation is having a dramatic effect on vitamin D status. However, we did not look at sun holiday travel which could explain some of the variation and has been associated with better vitamin D status in older Irish adults[10,34]. Similar to our study, non-white ethnicity has been found to predict lower rates of deficiency in England[34] and better vitamin D status in European populations at a similar latitude[35].

In Ireland, overall, about 5 % of the population are non-white and this demographic has increased in recent years[36]. Routine vitamin D supplementation for this section of the population is advisable as it has been found to be more effective than sunlight exposure for treating deficiency[37] and is currently recommended by the European Calcified Tissue Society[38]. Importantly, the vitamin D requirements for non-whites have been estimated to be much higher than the standard RDA advised in Ireland and by most international agencies. For example, maintaining a winter serum 25(OH)D ≥ 30 nmol/l in 97·5 % of individuals who are of South Asian and Black ethnicity would require an estimated respective daily vitamin D intake of 27·3 μg (1092 μg) and 33·2 μg (1328 μg)[31]. Public health information promoting dietary and supplement advice targeting this ethnic population in Ireland may be needed to address this deficiency.

Sun exposure

We found those who avoided sun exposure were up to twice as likely to be deficient while conversely greater body exposure when outside was associated with higher 25(OH)D concentrations and less deficiency in summer. This is in keeping with other Irish research which found that sun enjoyment was predictive of vitamin D status in older adults[4,10] and in patients with lupus[39]. Sun-seeking behaviours have also been identified as influencing vitamin D status in Irish and European women and children[40,41]. Our study indicates that summertime deficiency was halved in those with high *v.* low body exposure. Body exposure (days with sun exposed upper body) has been positively correlated with 25(OH)D at a similar latitude[42]. While there are concerns about skin cancer risk, moderate sun exposure has been shown to make up for deficiency in those who consume relatively low vitamin D[43]. Furthermore, for white-skinned people in the UK and similar latitudes, spending 9 min outdoors at lunchtime from March to September was estimated to be sufficient to maintain 25 nmol/l throughout winter[44]. Consistent with this, we found no difference in vitamin D status in those who spent more than 30 min in peak sunshine in the same period. We also identified that sunscreen users had better vitamin D status which can be considered a proxy for sun exposure with similar findings also reported in the Irish population[15,45,46] and at similar European latitudes[47,48]. While our study only explored vitamin D status in Dublin, other Irish studies have detected variations in deficiency by geographical location[7] that could be explained by differences in UVB availability due to latitude[4].

Vitamin D knowledge and indications for testing

Despite a surge for vitamin D testing and increasing costs, there remains little evidence on the indications for assessing 25(OH)D status. In a recent Irish study, a high proportion (a third) of vitamin D retests were found to be inappropriate, resulting in

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considerable unnecessary expenditure; however, no information was available on testing indications[21]. In this study, routine health checks accounted for a third of the reasons for testing, though this is not recommended and is considered inappropriate[49]. Additionally, 19 % reported other reasons including fatigue which are also not recognised as a valid clinical indication. Our results are similar to the UK and the Netherlands where 70–77 % of testing was considered inappropriate[50,51]. Patient reassurance has also been found to be a key driver of testing by general practitioners which is consistent with our finding that 'patient requests' were the most frequently declared other reason for testing[51].

We found that half (46 %) had no knowledge of any RDA recommendations, though a third (32 %) felt it was higher (≥ 20 µg/d) and 4 % lower (≤ 5 µg/d). Better vitamin D knowledge has been associated with increased likelihood of taking supplements[52], though supplement use has been found to be relatively low (10–17 %) in Ireland[5,7] suggesting a low level of concern for deficiency. However, during the COVID pandemic there is some evidence to suggest increased supplement use in Irish adults and possible improvement in vitamin D status[53]. Indeed, a publicised report by Irish researchers in April 2020 recommended a higher daily vitamin D intake of 20–25 µg (800–1000 µg) during COVID for adults aged > 70[54] so some knowledge of higher RDA's than advised by the FSAI might be expected. The majority (86 %) of respondents cited vitamin D as being important for bone health, similar to other studies[52,55]. Perhaps surprisingly, the second most common health association (66 %) was for immunity/COVID. This likely reflects media coverage during the pandemic of research on vitamin D's possible beneficial effects on COVID infection[56]. Indeed, trend analysis indicates there was a peak in Google searches for vitamin D coinciding with the first COVID wave in Ireland (March 2020) and during a subsequent wave (January 2021)[57]. The only other research was based on a small sample (*n* 112) of pregnant women attending a maternity hospital and found that 71 % had insufficient knowledge, with just 10 % recognising supplements as a source[12]. While there was good awareness of the benefits for bone and immune health, there is poor knowledge of the vitamin D RDA and little understanding of the indications for testing. This suggests that better awareness may help to improve vitamin D intake and status.

Strengths and limitations

This is the first study of its kind to explore multiple determinants of serum vitamin D in Irish adults including dietary intake, ethnicity and measures of sun exposure. It also adds to the limited research on adult knowledge and perceptions of vitamin D in Ireland and is the first to investigate indications for testing. However, as the study participants were selected from a sample of patients who had their vitamin D tested by their general practitioner, it may not be representative of the wider population. In particular, there may have been information bias as participants may have been aware of their vitamin D test results. Additionally, there may be also exclusion bias given that a significant proportion of adults did not return our questionnaire, though our response rate is in keeping with other studies using a similar methodology[58]. Finally, there may be recall bias as regards the recollection of food and supplement intakes when completing the FFQ.

Conclusion

We found, in a convenience sample of Irish adults, the biggest predictors of deficiency were low vitamin D intake (< 10 µg/d) ($P < 0{\cdot}001$) and non-white ethnicity ($P = 0{\cdot}006$), while it was twice as likely in those who were sun avoiders ($P = 0{\cdot}022$). In particular, deficiency in winter was twice as likely in those who of non-white ethnicity and was also more prevalent in those with lower body exposure when outside. Dietary sources of intake were small but still associated with better vitamin D status. However, the vast majority (81 %) who met the RDA were taking supplements. More than a third of vitamin D testing was for non-clinical indications, and the majority were not aware of the current RDA. Public health policy should be considered to improve vitamin D intake, especially in those of non-white ethnicity and with reduced sun exposure.

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Supplementary material

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Vitamin D deficiency in an northern, unfortified population - the perfect storm on the horizon?

Helena Scully[1], Dr Eamon Laird[2], Dr Martin Healy[3], Dr Kevin McCarroll[1], Prof J Bernard Walsh[1]

[1] Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin 8, Ireland.
[2] School of Medicine, Trinity College Dublin, Dublin 2, Ireland.
[3] Department of Biochemistry, St James's Hospital, Dublin 8, Ireland.

SCAN ME

Introduction: Vitamin D deficiency (VDD) is detrimental to bone health, playing an intrinsic role in osteoporosis and rickets. Recently it has been linked to morbidities including inflammation, CVD and cognition (1,2) . Most vitamin D (90%) is made by the action of UVB light on the skin, this is reduced in northern latitudes (>42°N). It is essential to ascertain the extent of VDD in an Irish cohort. The study aim is to investigate vitamin D status in a population of GP requested samples within the St James Hospital (SJH) catchment area.

Materials & Methods: The SJH catchment area (53°N) includes Dublin City, County Dublin and Eastern Leinster. 25(OH)D concentrations (measured by LC-MS/MS) from GPs requests for 2014-2018 were analysed. Results were tabulated in each postal district with percentage of samples deficient (<30nmol/L), insufficient (31-50nmol/L), and sufficient (>50 nmol/L). This data was further stratified by age (18-50, >50 years) and gender and analysed by Chi square.

Results: VDD (<30nmol/L) was prevalent in 15.7% of the population (n=35,289), with 23.3% insufficient (31-50nmol/L). The lowest socioeconomic areas (Dublin 1, Lucan, and Dublin 8) had a higher (p<0.0001) proportion of VDD (27%, 23.1% and 20.9%, respectively). VDD frequency across locations and seasons is shown in Figure 1. The geometric mean 25(OH)D concentration in the population was 53.92 nmol/L (SD 30.66). Males and those age 18-50 years were most deficient (Table 1).

Table 1- Vitamin D Deficiency by Age and Sex.

		Geometric Mean nmol/L (±SD)	Summer %<30 nmol/L	Winter %<30 nmol/L	P Value
Age	18-50yrs	48.8 (29.6)	17%	23%	0.000
	>50yrs	59.8 (30.7)	10%	13%	0.000
Sex	Males	49.9 (29.6)	15%	22%	0.000
	Females	55.6 (31.2)	13%	17%	0.000

Discussion: This study indicates that VDD remains prevalent in an Irish population, with large variations across Dublin and surrounding areas. Year-on-year analysis illustrates a greater prevalence of vitamin D assessment, however no improvement in vitamin D status was shown over time (data not shown). As such, further analysis are planned to explore factors contributing to VDD in this cohort.

Take Away: 1) Nearly 40% of the population were vitamin D deficient (<30 nmol/L) or insufficient (31-50 nmol/L).
2) Those at greatest risk are young males in lower socioeconomic areas in winter.
3) Demand for vitamin D analysis is increasing, with no change in status over time.
4) Highlights the need of national public health strategy to mandate for fortification to address this widespread deficiency.

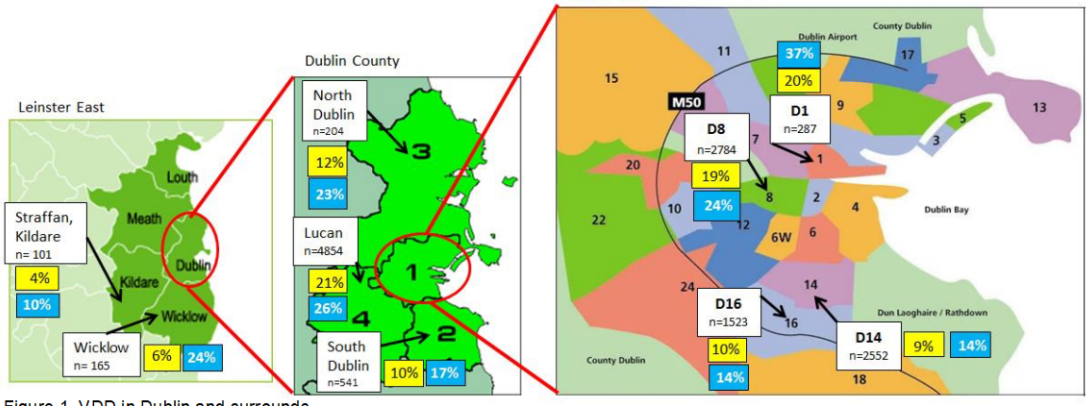

Figure 1. VDD in Dublin and surrounds.

References:
Laird E, et al., (2014) Vitamin D deficiency is associated with inflammation in Older irish adults. https://doi.org/10.1210/jc.2013-3501
Kheiri B, et al. (2018) Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. https://doi.org/10.1186/s40885-018-0094-8

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Vitamin D in childhood- high rates of deficiency in a cohort of Irish Children

School of Medicine

Helena Scully[1], Dr Martin Healy[3], Prof J Bernard Walsh[1], Dr Vivion Crowley[3], Dr Kevin McCarroll[1], Dr Eamon Laird[1,2]
[1] Mercers Institute for Research on Ageing, St James's Hospital, Dublin 8, Ireland
[2] School of Medicine, Trinity College Dublin, Dublin 2, Ireland
[3] Department of Biochemistry, St James's Hospital, Dublin 8, Ireland

Introduction: Vitamin D is essential for bone health, including the uptake and metabolism of calcium. Childhood/adolescence are periods of intensive bone growth, with vitamin D deficiency causing improper bone mineralisation, resulting in rickets. Evidence suggests that rickets prevalence is increasing globally[1], with levels in the UK the highest seen in five decades[2]. Vitamin D intakes were inadequate (<5ug/day) in 94% of 600 Irish children age 5-12 years[3] and teenagers (n= 428, 13-18yrs <10ug/day)[4]. The aim is to assess vitamin D status in a sample of Irish children and adolescents (1-17 years)

Methods: We selected children (age 1-17 years) from a sample of GP requested 25-hydroxyvitamin D (25(OH)D) tests analysed at St James's Hospital (SJH) between 2014-2020. The SJH catchment area (53°N) includes Dublin City, County and Eastern Leinster. Serum 25(OH)D concentrations were measured by LC-MS/MS. We identified prevalence of deficiency (<30nmol/L) and insufficiency (30-49nmol/L)[5] and stratified by age (<12 years, >12 years), gender and season (Winter; Dec-May vs. Summer; Jun-Nov). Data was analysed using Chi-square and ANOVA tests as appropriate.

Figure 1. Vitamin D Status in Winter

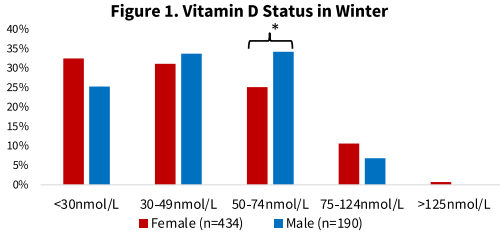
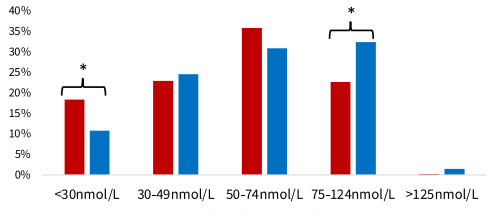


Figure 2. Vitamin D Status in Summer



*indicates significance (p<0.05) analysed by Chi-square.

Results:

- We identified N=1,269 children, 69% female, 11% under 12.
- Vitamin D deficiency (VDD) was prevalent affecting with 23% and 28% with insufficient vitamin D status.
- The geometric mean 25(OH)D was 43.81 nmol/L.
- Deficiency and insufficiency were more common in winter vs. summer (30% vs 16%, p<0.001), (32% vs. 23%, p<0.001, respectively) **(Figures 1 & 2).**
- Those over 12 years were more likely to be deficient (24% vs. 16%, p=0.033) as were girls vs. boys (25% vs. 18%, p=0.003) **(Figures 3 & 4)**.

Figure 3. Vitamin D Status in Under 12s

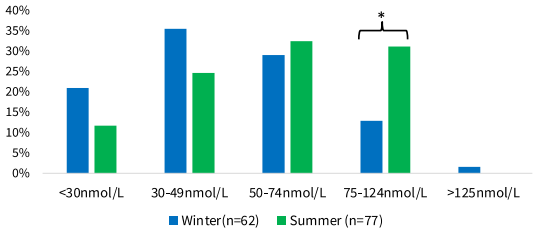
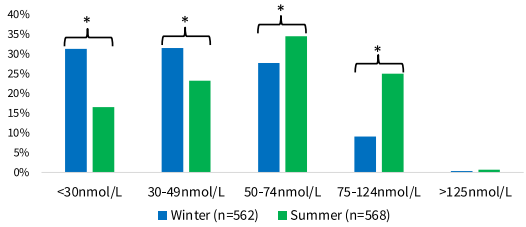


Figure 4. Vitamin D Status in Over 12s



*indicates significance (p<0.05) analysed by Chi-square.

Conclusion:

- This is the largest study of vitamin D status in Irish children.
- Low vitamin D status (<50nmol/L) is highly prevalent (51%), with girls, those over 12 years and those assessed in winter most at-risk.
- Irish children's vitamin D status in this study is similar to other EU countries and higher than previously published results in Irish adults[6].
- Public health measures, such as a policy for systematic targeted food fortification, should be considered to address this issue in children.

References:
1. Creo AL, Thacher TD, Pettifor J et al. (2017) *Paediatr Int Child Health 37*(2) 84-98.
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Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
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School of Medicine

Vitamin D retesting by General Practitioners: a factor and cost analysis

Helena Scully [1], Eamon Laird [1,2], Martin Healy [3], Vivion Crowley [3], James Bernard Walsh [1], Kevin Mc Carroll [1]

[1] Mercers Institute for Research on Ageing, St James's Hospital, Dublin 8, Ireland
[2] School of Medicine, Trinity College Dublin, Dublin 2, Ireland
[3] Department of Biochemistry, St James's Hospital, Dublin 8, Ireland

Introduction: Vitamin D testing by Primary Care doctors is increasing as are the associated costs[1]. This places an increased workload on laboratories and healthcare systems though there is little data on vitamin D testing patterns in Ireland. This study aims to investigate the factors associated with vitamin D testing by Irish General Practitioners (GPs) including age, gender and location and resulting costs.

Methods: This is a retrospective analysis over 5 years (2014-2018) of GP requested 25-hydroxyvitamin D (25(OH)D) results at a major city hospital in Dublin, Ireland. Those with one test were compared with individuals who had follow up testing (retested). Deficiency (<30nmol/L), insufficiency (30-50nmo/L and sufficiency (>50nmol/L) were calculated[2]. Inappropriate testing was defined as (1) retests <3 months of the first or initial test, (2) ≥2 retests within one year and (3) retests in those who were initially vitamin D replete (50-75 nmol/L). Data was analysed using Chi-square and ANOVA tests as appropriate

Results:

- We identified 36,458 patients (72% female).
- 22.8% patients were retested though all retests accounted for 27.2% of all vitamin D requests.
- Positive predictors of retesting were; female gender (p<0.001), age (60-69yrs, p<0.001), location (Co. Kildare, p<0.001), initial deficiency (p<0.001) or insufficiency (p<0.001).
- Vitamin D status improved on retesting, halving deficiency on first retest (9% vs. 18%, p<0.001) and dropping to 6% on further retests.
- Deficiency decreased between initial and first retest, and first and ≥2 retests in most age groups **(Figure 1)**
- 12.2% of retests were done within 3 months, one third (29%) had >2 retests within 1 year **(Figure 2)** and 57% were in those who were initially vitamin D replete.
- The annual estimated cost of inappropriate testing was €61,976.

Figure 1 – Vitamin D deficiency (<30 nmol/L) on retest by age category

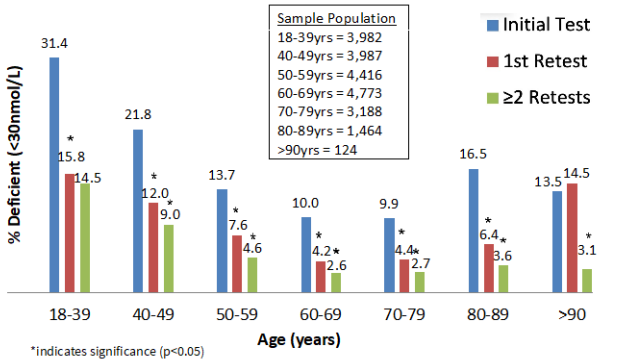
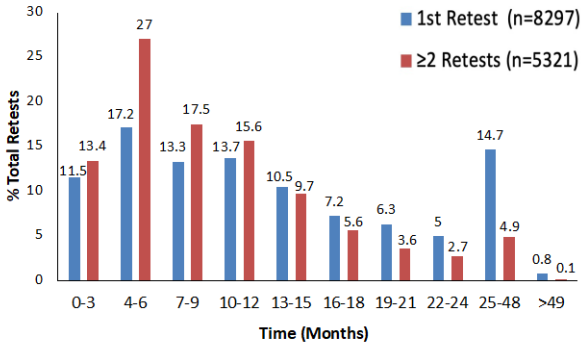


Figure 2 – Time difference between vitamin D retests



Take Home Points:

- 1 in 4 adults are retested for vitamin D by their GP, this varied by age, gender and location
- Over 10% of retests were inappropriately early (<3 months)
- 1/3 were too frequent (≥2 retests within 1 year)
- Over half (57%) were in replete individuals (>50nmol/L)
- Inappropriate testing costed over €60,000 annually
- Clear guidance for GPs on minimum retesting intervals are needed, as well as laboratory ordering systems to limit requests using pre-defined criteria.
- Population based strategies to reduce deficiency may be more effective than widespread testing.

References:
[1]Sattar N, Welsh P, Panarelli M *et al.* (2012) *Lancet (London, England)* **379**, 95.
[2]Institute of Medicine (IOM) (2011) Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press.; 2011.

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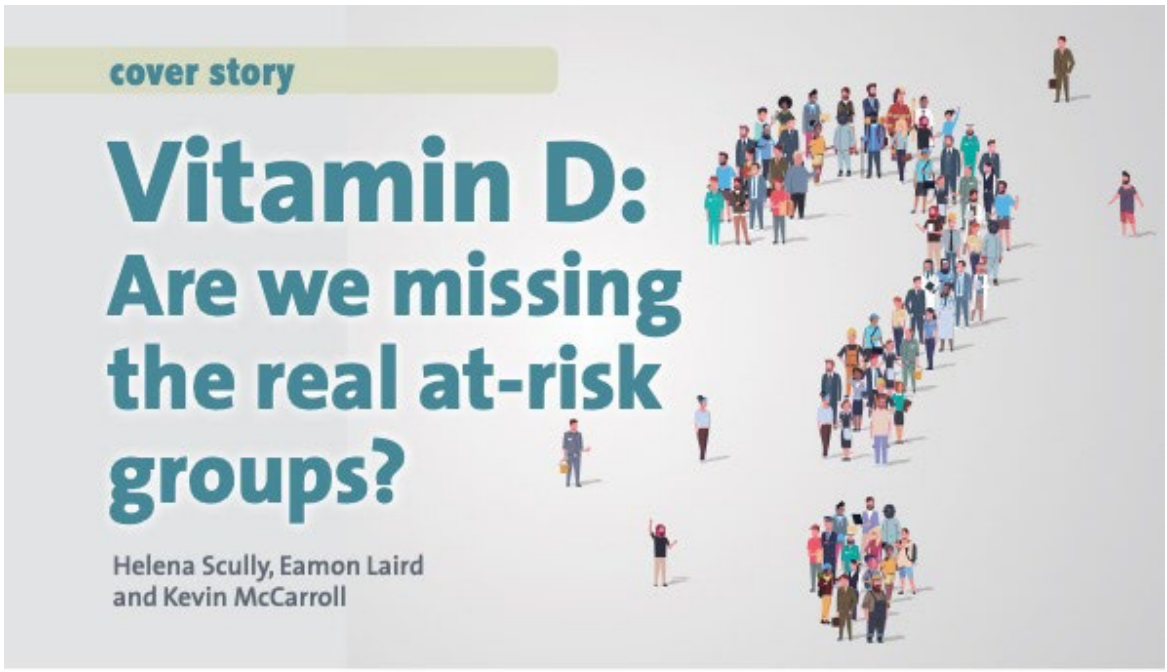
iv. Professional Communications

Vitamin D: Are we missing the real at-risk groups- *Cover story article in Irish Nutrition & Dietetic Institute- Nutrition and Dietetic Review Magazine* (Winter 2020 Edition)



cover story

Vitamin D: Are we missing the real at-risk groups?

Helena Scully, Eamon Laird and Kevin McCarroll

A recent Irish study revealed that young males and those living in poorer socioeconomic areas had the greatest risk of vitamin D deficiency

VITAMIN D IS A STEROID HORMONE that is endogenously synthesised via the action of sunlight on the skin. The majority of vitamin D is made this way, with limited selected dietary sources also contributing to our intake. In Ireland, we are at increased risk of vitamin D deficiency due to our northern latitude, which results in an inability to produce vitamin D from the sun between October and March. Other factors such as cloud cover, pollution, clothing, obesity and sunscreen use can reduce the amount of vitamin D that can be produced.[1]

When sun exposure is limited, we are solely reliant on a limited number of naturally rich sources of vitamin D in the diet. The best sources include oily fish such as wild salmon, mackerel and trout, egg yolk, fortified dairy and cereals, and sun-ripened mushrooms. While vitamin D levels in red meat are relatively low, they contribute a considerable source to the Irish diet.[2]

Vitamin D is established in its role in bone and muscle health, contributing to the absorption of calcium and phosphate in the gut and aiding bone mineralisation. Inadequate vitamin D status can result in deficiency, which in some patients can contribute to fatigue, bone and muscle pain, and an increased risk of falls and fracture.[3] Long-term deficiency can cause improper bone mineralisation, leading to rickets in children and osteomalacia in adults. More recently, the role of vitamin D has been investigated in non-musculoskeletal conditions such as cardiovascular disease,[3] diabetes,[4] inflammation,[5] depression[6] and respiratory infections.[7]

The typical 'at-risk' groups for vitamin D deficiency are seen as older adults and females. Recent data from The Irish Longitudinal Study on Ageing (TILDA) has indicated one in eight older Irish adults (>50 years) are deficient while this increases to 46% in those aged >85 years.[8] However, little is known about the vitamin D status of the rest of the population and if it varies depending on location of residence.

The aim of our study was to assess

Figure 1: Vitamin D status across different age categories

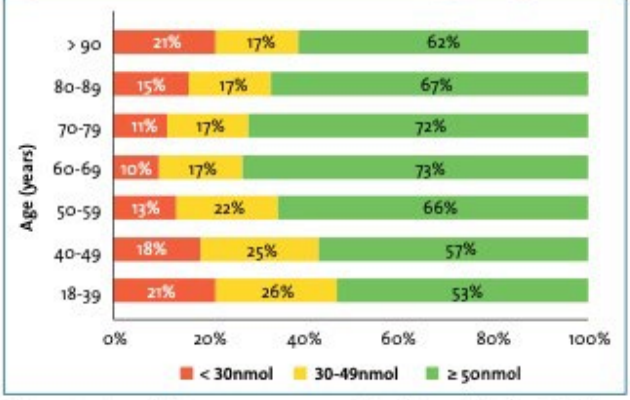
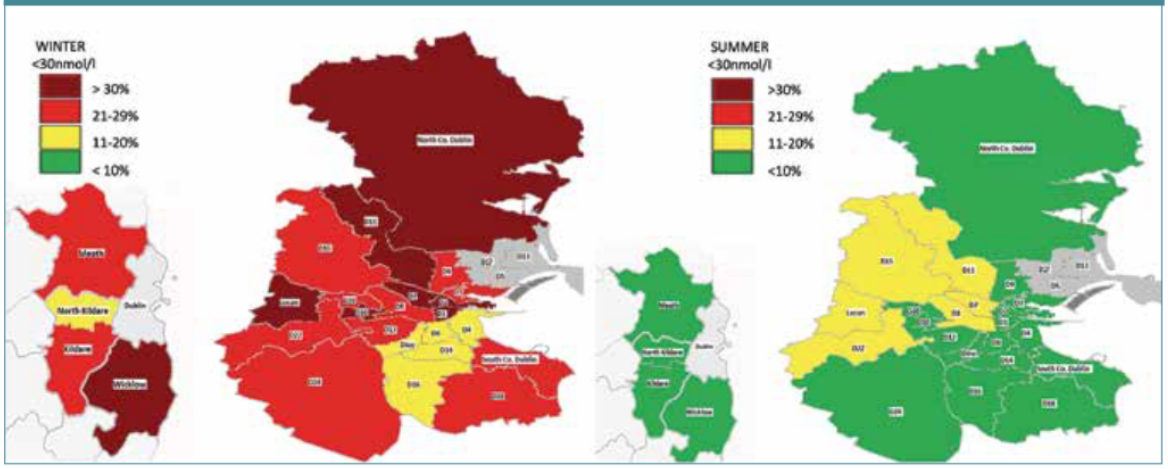


Figure 2: Geomap of 25(OH)D status of Dublin and surrounding counties in winter and summer



vitamin D deficiency (<30nmol/L) and insufficiency (30-50nmol/L) in a community-based population (N= 36,466) who had their vitamin D measured by the gold standard mass spectrometry by request of their GP at St James's biochemistry department. We then explored the effect of age, gender and location on vitamin D status.

Key findings

We observed that those in the youngest age category (18-39 years) had the lowest vitamin D status in the cohort, followed by those aged 40-49 years (*see Figure 1*). Both of these groups had between one-third and one-half of their populations with vitamin D <50nmol/L, indicating a large proportion of the population under 50 years are at risk of inadequate vitamin D status.

Women had a much better vitamin D status compared to men and were 32% less likely to be deficient (<30nmol/L), with males on average having an insufficient vitamin D status with a mean level of 49.7nmol/L. Using the novel technique of geomapping, vitamin D status was mapped for each sample by postcode or general area. This allowed for a geographical representation of vitamin D status across eastern Leinster (see *Figure 2*).

By splitting the cohort by season, clusters of vitamin D deficiency were detected across the study areas. This discovered large variations in vitamin D status in areas of close proximity. In winter, a cluster in south Dublin (Dublin 4, Dublin 6/6W, Dublin 14/16) was found to have greater serum levels when compared to areas in west, central and north Dublin (*see* 9).

For example, Dublin city centre (Dublin 1 and Dublin 2) had greater levels of deficiency at 37% and 34% respectively. However, the adjacent areas of Dublin 4 and Dublin 6 had nearly half the level of deficiency at 19%.

Differences across demographics and area

Dietary trends indicate that one in five young adults is either vegan, vegetarian or seeking to reduce animal products in their diet.[9] The reduction in meat, dairy and fish consumption is of concern as these are good sources of micronutrients including vitamin D. Younger adults are less likely to be meeting the recommended dietary intake of vitamin D or to take a supplement.[2] They are also more likely to be working indoors during the day compared to older adults and retirees, and may have less opportunity for skin synthesis.[10]

These trends are of particular concern as vitamin D is a requirement for healthy bone formation and that peak bone mass is accrued in the late teens and early twenties. A lack of this essential nutrient at this time increase the risk of failure to attain peak bone mass resulting in an increased risk of fragility fractures, falls and osteoporosis later in life. On the other end of the age spectrum, we found those in the oldest age categories (+80 years) had declining levels of vitamin D.

When factors such as; the natural decrease in the skin's ability to synthesise vitamin D, a reduction in dietary intake (through sensory change), increased frailty and reduced sun exposure are taken together, it's clear that this demographic has numerous risk factors for deficiency. These findings are reflected in the TUDA and TILDA longitudinal studies of ageing, which found levels of deficiency between 13.1-43.6%.[11,12]

In terms of the gender difference, our findings match a recent meta-analysis of 394 studies, which found comparable mean levels for men (49.7 versus 50nmol/L) and women (55.1 versus 56nmol/L) in a global study of vitamin D (13). The majority of our cohort were female, representing 72% of the total samples received, as similar to a study carried out in the west of Ireland.[14]

This is likely due to women having more health seeking behaviours than men, such as attending primary care with their GP.[15] Women are also more likely to be aware of the importance of bone health given the prevalence of osteoporosis, with greater targeting of prevention and treatment.[16] Furthermore women are more likely to be taking a dietary supplement containing vitamin D.[2,11] Women were also more likely to have a 25(OH)D level above 125nmol/l, which was most prevalent in Dublin 3 at 7%.

At the geomapping level, it is likely that socioeconomic status is a key driver of vitamin D status. It has previously been found that those with lower asset wealth are one and a half times more likely to be vitamin D deficient. This is likely due to factors associated with low socioeconomic status, such as access to quality food containing vitamin D, less sun holiday travel and potentially higher rates of obesity and smoking, which can affect vitamin D concentrations.[11] When vitamin D status was assessed by season of measurement, the situation deteriorated in winter as half the population had either a deficient or insufficient status.

Despite an increase in the number of samples received over the five-year period, there was no improvement in vitamin D status. On average, one in six were deficient and one in four were insufficient, indicating that a large proportion of the population had inadequate vitamin D status. These results show that while demand for vitamin D testing is increasing, this has not appeared to translate to an improved vitamin D status. The number of individuals

cover story

who had potentially excess levels of vitamin D (>125nmol/l) was relatively stable over time, with an average 3% of the cohort meeting this level, with men being less likely to be in excess compared to women.

Future considerations

This study identified a high level of vitamin D deficiency in Dublin and surrounding counties, particularly in the winter in which half had insufficient levels of vitamin D (<50nmol/l). Furthermore it found that certain groups of the population, such as young males and those living in poorer socioeconomic areas, had the greatest risk of deficiency. These groups up to now have not been considered 'at risk' of vitamin D deficiency and have been largely ignored in terms of policy or guidance.

As our opportunity for sun exposure diminishes as winter sets in, it is particularly important, especially this year, to ensure adequate vitamin D intake. The Covid-19 pandemic has greatly reduced our opportunity for sun exposure due to lockdown restrictions, cocooning and advice against foreign holiday travel for much of the population.

While no studies definitively confirm the effect of vitamin D in the prevention or treatment of Covid-19, there is strong circumstantial evidence that supports its beneficial role, not least its effect on inflammation and respiratory conditions.[17]

Having detected a large proportion of vitamin D deficiency in the community, it is prudent to recommend that individuals focus on meeting the recommended level of 10ug (400i IU) per day whether achieved by diet or in combination with supplements. It is also crucial that the real at-risk population groups are targeted for supplementation or education to increase dietary intakes to avoid the long-term repercussions of inadequate vitamin D.

Helena Scully is the Mercers Glanbia Bone Fellow, Eamon Laird is a research fellow and Kevin McCarroll is a consultant physician, all at St James's Hospital in Dublin

Full Paper details: Geomapping Vitamin D Status in a Large City and Surrounding Population-Exploring the Impact of Location and Demographics. Nutrients 2020 Aug 31;12(9):E2663. doi: 10.3390/nu12092663.PMID: 32878330

This research was partially funded by Mercers' Institute and Glanbia Ireland. The funders have no role in study design, data collection and analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results

Table: Vitamin D food sources per 100g/100ml

Food Sources	Vitamin D (per 100g/100ml)
Fish and shellfish	
Herring, grilled	16.1ug
Wild salmon, baked	10.1ug
Smoked salmon	8.9ug
Mackerel, grilled	8.5ug
Rainbow trout, baked	8.2ug
Farmed salmon, baked	7.3ug
Sardines, grilled	5.1ug
Tuna, grilled	3.1ug
Tuna, tinned in brine	1.1ug
Milk and milk products	
Supermilk, (Whole or Low fat)	2ug
Actimel	2ug
Animal products	
Eggs, chicken	3.2ug
Corned beef, canned	1.3ug
Sausages, pork, grilled	1.1ug
Pork loin	0.8ug
Roast beef	0.8ug
Roast pork	0.7ug
Bacon rashers	0.6ug
Non-animal based	
Benecol spread	7.2ug
Sun-ripened mushrooms	7ug
Low Low spread	5ug
Fortified cereals	4.7ug

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Clinical Vitamin D

GP advisory: The prevalence and determinants of vitamin D deficiency

In his advisory to general practitioners, **Dr Kevin McCarroll**, Clinical Senior Lecturer and Consultant Physician at St James's Hospital, Dublin, brings up causes, recognising at-risk groups, prevention, and treatment of vitamin D deficiency

Vitamin D has become the focus of huge interest in recent years on the back of increasing medical literature highlighting high rates of deficiency in the population. More recently an increasing body of circumstantial evidence supports vitamin D plays a beneficial role in combatting the effects of Covid-19.[1] In fact, to date there are more than 250 peer-reviewed studies published on the topic of 'Vitamin D and Covid-19'. Vitamin D is widely regarded as being important for a healthy immune system and has also been associated with having a beneficial effect in cancer, autoimmune, cardiovascular, and respiratory diseases, as well as in depression and cognitive impairment.[2]

What constitutes vitamin D deficiency has been a matter of controversy and is defined only in relation to optimal bone health outcomes.

A 25-hydroxyvitamin D level of less than 30 nmol/l is generally considered to represent deficiency and can cause rickets in children, osteomalacia in adults and can also result in secondary hyperparathyroidism.[3]

Levels between 30-50 nmol/L represent possible deficiency and may be deleterious to bone health though other factors such as calcium and phosphate intake interact with vitamin D and play a role.

For this reason, levels in the 30-50 nmol/L range have been categorised as "insufficient".[4]

However, higher calcium intake appears to partially compensate for lower vitamin D status by reducing secondary hyperparathyroidism.[5]

Author

Dr Kevin McCarroll, Clinical Senior Lecturer and Consultant Physician at St James's Hospital, Dublin.

Co-author of *Geomapping Vitamin D Status in a Large City and Surrounding Population*, a study exploring impact of location and demographics on vitamin D status.

Above: Pictured at the launch of the Vitamin D Geomapping research programme in 2019 were (L-R) Senior Research Fellow at TCD School of Medicine, Dr Eamonn Laird; Consultant Physician at St James's Hospital, Dr Kevin McCarroll; Mercer Glanbia Bone Research Fellow at the TCD School of Medicine, Helena Scully; TCD Clinical Professor and Director of the Bone Health and Osteoporosis Unit at MISA, Prof J Bernard Walsh; and Principal Clinical Biochemist at St James's Hospital Dr Martin Healy

Vitamin D repletion

To ensure that one is vitamin D replete, it is prudent to maintain a level of 50 nmol/L[4] which should be the target in those with low bone density or osteopaenia / osteoporosis. Vitamin D levels up to 75 nmol/L have been associated with more optimal suppression of serum parathyroid hormone (PTH), bone turnover markers and bone density in several studies though evidence is mainly observational and definitive data is lacking.[3]

The United States (US) Endocrine Society defines vitamin D insufficiency as a level between 50-75 moll/L[6] though this is not widely accepted by other bodies including the US Institute of Medicine and the Royal Osteoporosis Society in the United Kingdom (UK).

In Ireland and countries above 32° north latitude, little or no vitamin D synthesis occurs between the months of November to March as ultraviolet B (UVB) radiation is too weak, giving rise to the so-called "vitamin D winter".

In fact, vitamin D levels are typically highest in August / September at the end of the summer and lowest in February / March.

Indeed, the level usually drops by about 30 per cent between seasons so this should be factored in when interpreting results.[7]

Role in falls prevention

Beyond bone health, there is strong evidence from randomised controlled trials that vitamin D may reduce falls which may be mediated by its effect on muscle strength.

Studies point to a benefit in those who are vitamin D deficient and have a history of falls though a level of 60 nmol/L may be required.[8] Levels up to 75 nmol/L have also been associated with better performance in tests of physical function including gait speed.[9]

For this reason, a level of up to 75 nmol/L is recommended for older adults by some bodies including the American Geriatric Society, particularly for those who are frail and at risk of falls and fractures.[10]

This remains controversial, though a level of 75 nmol/L is safe and has not been associated with any adverse effects. Levels above 75 nmol/L are probably surplus to requirement and confer no clear benefit while levels above 125 nmol/L may be harmful.[4] Vitamin D toxicity is rare and is usually associated with levels above 250 nmol/L.[3]

Prevalence of vitamin D deficiency

In Ireland, overall, 13.1 per cent of the population older than 50 are vitamin D deficient (<30 nmol/L) based on findings from The Irish Longitudinal Study of Ageing (TILDA).[11]

In the same study, deficiency affected nearly one in four in the winter with the greatest prevalence (37%) in those aged over 80. In addition, there were regional variations with higher rates of deficiency in the north and west of the country. Similarly, in an Irish study (n=1,316) of frail, older adults attending outpatient clinics, deficiency (<30 nmol/L) had a reported prevalence of 33 per cent with about 75 per cent having levels below 50 nmol/L.[7]

It has also been estimated that 27 per cent of over-70s that were cocooning may be deficient.[12]

Geomapping vitamin D status

The largest study to geomap vitamin D status in Europe (n= 36,466) published recently by researchers from Trinity College Dublin and Mercer's Institute for Successful Ageing (MISA) focused on the prevalence of deficiency in Dublin and the Leinster area based on general practitioners' (GPs') vitamin D requests.[2] Using the technique of geomapping, vitamin D status was mapped for each sample by postcode or general area.

Unlike many studies which included older adults, it identified the highest rate of deficiency (21%) in those who were younger (18-39 years) followed by those in the age category (40-49 years).

Furthermore, between one-third to one half of adults aged less than 50 had levels below 50

▶ 34

◀ 32

nmol/L. Women also had better vitamin D status compared to men and were 32 per cent less likely to be deficient (< 30 nmol/L).

It also discovered a striking variation in vitamin D status between areas of proximity with those living in poorer socioeconomic districts typically having lower status.

For example, in winter, areas in South Dublin (Dublin 4, Dublin 6/6W, Dublin 14/16) were found to have greater levels when compared to west, central and north Dublin.

In Dublin city centre (Dublin 1 and Dublin 2) there were also greater levels of deficiency at 37 per cent and 34 per cent though in the nearby areas of Dublin 4 and Dublin 6 prevalence was nearly half this at 19 per cent.

Differences in vitamin D status across demographics and areas

There are several factors that likely account for the big variation between areas including differences in dietary vitamin D intake and sun exposure. Local differences in population demographic and ethnicity affecting the capacity for cutaneous vitamin D synthesis are also factors.

Higher prevalence of deficiency in Donegal and in the northwest is also likely due to lower UVB exposure as result of greater cloud cover.

Studies indicate that about one in five younger adults are either vegan, vegetarian or seeking to reduce animal products in their diet.[13] However, meat, vitamin D-fortified dairy and fish consumption account for a significant proportion of overall dietary vitamin D intake.[14]

Shiftworkers may also lose out on the opportunity for sun exposure which has been associated with a higher prevalence of deficiency.[15]

Socioeconomic status (SES) is also linked with deficiency as borne out by several studies including TILDA, where lower asset wealth increased the risk by a factor of 1.5.[11]

Foods that naturally contain vitamin D are limited and can be more expensive including oily fish. Sun holiday travel which can also boost vitamin D status may also be less frequent in subgroups of the population.[2,7]

Lower SES is also associated with higher rates of obesity which probably lowers vitamin D levels as a result of sequestration in fat tissue.

Smoking is also a factor, as it has been independently associated with lower vitamin D in most studies, though the mechanism is not understood.[11,16]

Older adults have a higher risk of deficiency due in part to increasing frailty and less sun exposure. The capacity of the skin to synthesise vitamin D may decline by as much as 75 per cent with age, possibly because of reduced levels of cutaneous 7-dehydrocholesterol, the precursor of pre-vitamin D.[17]

Deficiency is also more likely in those with more pigmented skin where longer sun exposure is needed for vitamin D synthesis due to increased UV absorption by cutaneous melanin.[17]

Vitamin D deficiency is often picked up on blood tests in those who have no or non-specific symptoms. However, severe deficiency can give rise to generalised aches and pains and osteomalacia, which can be exacerbated by low calcium intake.

Who should be tested?

Guidelines vary though 'at-risk' groups should be considered for testing. These include frail older adults, those with minimal sun exposure, malabsorption syndromes, unexplained musculoskeletal symptoms, and low bone density.[3]

Consider rechecking levels to ensure adequate response to treatment, especially if compliance with supplements is in question or in those with osteomalacia. If using daily supplements, levels should not be checked for at least three months — the time taken to reach steady state.

Prevention and treatment

Whilst dietary sources of vitamin D are limited, they account for a significant contribution to overall status, especially in the winter. Rich sources include oily fish, sundried mushrooms, vitamin D-fortified milk and breakfast cereals.[3]

Some fortified foods also have the added advantage of containing additional calcium, which along with vitamin D, is important for bone health.

Oral vitamin D supplements (prescribed or over the counter) are also readily available. In most cases, 800-1,000 IU vitamin D3 daily will be sufficient to maintain a level of 50 nmol/L though higher doses will be required if there is poor gut absorption or liver disease. A variety of licensed treatments are available including daily (800 IU or 1,000 IU), once-weekly (7,000 IU) or once-monthly (25,000 IU).

Therapy with 50,000 IU once weekly for about six weeks can be used for more rapid correction of deficiency followed by maintenance supplements.[18]

As a rule of thumb, 25-hydroxyvitamin D levels should rise by at least 2.5 nmol/L per 100 IU given[19] so 800 IU daily should result in an increase by about 25 nmol/L. In those with low bone density, total calcium intake should be at least 700-1,200 mg daily.[20] If additional calcium is required, combined vitamin D / calcium supplements can also be used with a variety of prescription doses available.

While there are different recommendations for daily or equivalent daily vitamin D intakes, the US Institute of Medicine advises 600 IU/day for those aged between 9–70 and 800 IU/ day in those aged older than 80.[4] DIT

References available upon request.

Information

The findings of 'Geomapping Vitamin D Status in a Large City and Surrounding Population' were published in the journal *Nutrients* 2020, 12(9); published August 31, 2020; and can be viewed at: https://www.mdpi.com/2072-6643/12/9/2663.

The study was partially funded by MISA and Avonmore and builds on a longstanding collaboration. Avonmore has no role in study design, data collection and analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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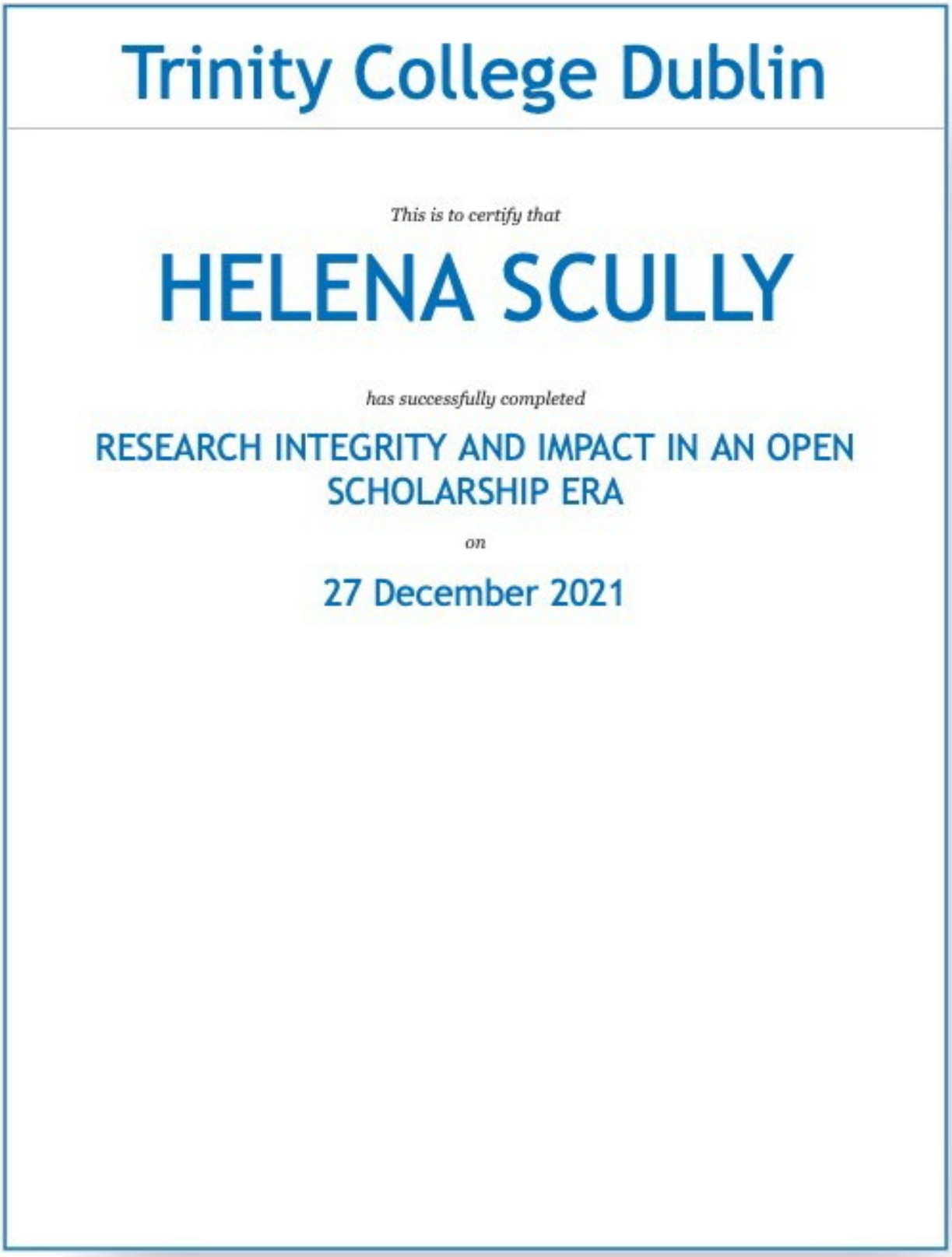

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27 December 2021