Research Project Draft Protocol December 2011

Vitamin D and Premature Mortality – a Systematic Review of the Evidence

Background

In 2010, Walsh et al published ''Investigating a Glasgow Effect': why do equally deprived UK cities experience different health outcomes?'[1]. In this study, the authors compared mortality data for Glasgow, Liverpool and Manchester. Despite having comparable levels of deprivation, all-cause mortality was found to be 15% higher in Glasgow. Premature mortality, defined as deaths under 65 years, was 30% higher, and higher still in the 15-44 years age band. The emergence of a widening gap in mortality was also seen, with death rates improving more slowly in Glasgow than in the other cities from 1980 onwards.

A number of explanations for this phenomenon have been suggested and are discussed in the report, 'Accounting for Scotland's Excess Mortality: Towards a Synthesis'[2]. Greatest consideration is given to social, economic and cultural factors, however the authors acknowledge that no one individual factor seems to account for Glasgow's poor health record. It has been suggested that climate may have a role, with the low levels of sunlight experienced in the West of Scotland predisposing the population to vitamin D deficiency[3].

The role of vitamin D in bone metabolism and prevention of rickets is well-established, however, a deeper understanding is emerging about its effects on cell proliferation and differentiation, alongside growing interest in the association between vitamin D levels and a range of chronic diseases, including cardiovascular disease, cancer and diabetes. There is limited evidence that vitamin D levels are inversely correlated with mortality[4-6], however many confounding factors must be considered before this relationship can be assumed to be causal. It may be that sun exposure, and increased synthesis of vitamin D, is associated with increased physical activity, which may act independently to reduce cardiovascular and other risks[6]. Also, obesity is known to be associated with lower levels of vitamin D, leading to speculation that low vitamin D status may be a risk 'marker' rather than a risk factor[5].

The main source of vitamin D is skin synthesis, with comparatively small amounts obtained from dietary sources[7]. Vitamin D is synthesised in the skin from 7 dehydrocholesterol under the action of sunlight[8]. In the liver, Vitamin D3 (cholecalciferol) is converted to 25-hydroxycholecalciferol (25-OHD3), which is in turn converted to the more active 1,25-dihydroxycholecaliferol (calcitriol, 1,25-(OH)2D3) in the proximal tubules of the kidney. The active form, 1,25-dihydroxycholecalciferol has a central role in the regulation of calcium metabolism. However, 25-hydroxycholecalciferol is regarded as the most accurate serum marker of vitamin D status due to its relatively long half-life[9].

There has been a lack of consensus about optimum vitamin D levels for health. Concentrations of less than 25 nmol/L (nanomoles per litre) are regarded as deficient and a risk factor for bony pathology, in the form of rickets in children, or osteomalacia in adults,

however it has been suggested that much higher levels (> 75 nmol/L) are necessary for maximal bone health[10]. In the USA, the Institute of Medicine has suggested a recommended daily intake (RDI) of 600 IU for infants, children and adults, and 800 IU for those aged over 70[9;11]. In contrast, in the UK, the Department of Health does not provide an RDI, instead suggesting use of supplements in individuals at risk of deficiency: children under 5, the over 65s, pregnant or lactating females, individuals with limited exposure to sun and people with darker skin tones[12]. NHS Health Scotland has issued similar advice for Scots[13].

Vitamin D deficiency is widespread in the UK, regardless of the cut-off level used to define it. In Hypponen and Power's UK-wide study of vitamin D levels in 7500 participants from the 1958 British birth cohort, 87% had concentrations below 75 nmol/L during winter months[14]. It has been suggested that individuals at higher latitudes who experience less sun exposure will be at increased risk of vitamin D deficiency. Furthermore, cloud cover further limits UV penetration, raising the question of whether the west of Scotland population, with its often cloudy weather, is at particular risk[7]. Certainly, in Hypponen and Power's study, Scottish participants were at increased risk of deficiency (OR 2.38) compared to those resident in the South of England[10]. A subsequent Scottish study of 2235 healthy adults found that 92% had levels less than 75 nmol /L[7]. No specific comparisons of vitamin D levels in the west of Scotland with other regions have been identified.

The evidence of variation in vitamin D levels with latitude is not consistent, however. In fact, some studies have shown a positive relationship between vitamin D and northern latitude[15;16]. This may be due to the effect of melanin on cholecalciferol synthesis, which means that individuals with more pigmented skins are less efficient at synthesising vitamin D[17], or may reflect differing sunbathing practices in warmer climates.

Changes in lifestyle may also be important in limiting sun exposure. Fears over child safety and changing leisure pursuits may mean more free time spent indoors. There is a trend away from exposing the legs via short trousers or skirts in school children, except during summer months. Increased awareness of the risks of sun exposure has both changed sunbathing habits and increased use of sunscreen. Although dietary sources provide only minimal vitamin D, it may be that changes in consumption of oily fish, compared with previous generations, is also important. It is possible that these changes are associated with temporal changes in population vitamin D levels, although a lack of historical data makes meaningful comparisons difficult.

Why this question is important

A growing body of evidence suggests that vitamin D levels are inversely correlated with mortality. However, there is as yet a lack of robust evidence in the form of randomised controlled trials of vitamin D supplementation. The existing observational evidence is also subject to confounding and a lack of clarity about whether any association is causal.

There is the potential for harm to arise if action is taken to increase population vitamin D levels. An association with pancreatic cancer has been demonstrated at levels greater than 100 nmol/L[18]. Furthermore, the incidence of melanoma and other skin cancer, which are associated with exposure to solar radiation (a likely means of increasing population vitamin D), continues to rise[19]. Therefore the balance between the potential harms of vitamin D deficiency and the means of decreasing any deficiency (whether through exposure to solar radiation or dietary change) needs to be informed by clearer evidence of the risks of vitamin D deficiency.

There is particular interest in this research question in Scotland, since it has been suggested that vitamin D deficiency may be (at least partially) responsible for the higher mortality in comparison to other parts of western Europe, and the higher mortality in England and Wales after accounting for deprivation (i.e. the Scottish effect).

Previous systematic reviews

Two systematic reviews have investigated the effect of vitamin D supplementation on total mortality[20;21], and found that supplementation was associated with a modest reduction in mortality. Autier's review was subsequently reanalysed by Chung et al as part of a wider systematic review on vitamin D and calcium and health outcomes[22]. The studies included in these reviews involved predominantly elderly participants who were participating in trials investigating the potential of vitamin D supplementation to reduce fractures. I am unaware of any previous reviews of the association between vitamin D and premature mortality, either published or in progress.

Aims and Objectives

Aim of Project:

To determine whether there is evidence of an association between serum vitamin D and premature mortality, and the nature of any association.

Objectives

To develop a strategy for, and perform, a comprehensive literature search that enables identification of all relevant studies.

To screen all identified studies for relevance to the research question.

To critically appraise all relevant studies for potential sources of bias, error and confounding.

To extract relevant mortality data and apply appropriate statistical analysis in order to evaluate the precision of any association between vitamin D status and premature mortality, and to identify potential sources of publication bias.

To evaluate the evidence for any observed association being of a causal nature.

To draw conclusions about the potential for vitamin D deficiency to explain the premature mortality pattern in Scotland.

To reflect on the learning achieved whilst undertaking the dissertation.

Supervision

This project will be carried out by Lynne Rush. Dr Gerry McCartney will act as Project supervisor, with Dr David Morrison acting as an academic supervisor. David Walsh will also have continued input during the process. Regular meetings will be held throughout the duration of the project work.

Methods

This project will follow the usual stages of a systematic review, adhering to the PRISMA checklist[23].

Search Strategy

A database search strategy will be developed and discussed in collaboration with subject librarians from the University of Glasgow and NHS Health Scotland. The following databases will be searched: Medline (including non-indexed articles and articles in progress), Embase, the Cochrane Library and Web of Knowledge. The search will be restricted to human articles. No limitations will be imposed for year of publication or English language.

The results of the search will be de-duplicated using a reference management system.

Abstracts of articles identified by the initial database searches will be screened for relevance. Abstracts deemed irrelevant to the study question will be further screened by a second researcher. Full copies of relevant articles will be obtained for review, where possible, and considered for eligibility. Records of all excluded studies will be retained. The results of the database search will be summarised via a flow diagram.

The reference lists of the included studies will be searched for other potential relevant literature and papers listed as citing the eligible studies on will be reviewed for relevance.

Review articles will be used to identify relevant primary studies.

The indices of key journals will be searched for relevant studies.

The key authors in the field will be contacted to ensure relevant data not identified by search is included.

Relevant grey literature will be identified through a structured internet search using the search engines “Google” and “Google scholar”.

The search strategy may be amended at a later date, depending on manageability of the data found. Any changes to the initial strategy will be made explicit in the finished review.

Study Selection

Participants

All settings, i.e. hospital, clinic or community, in all countries, will be included. Both male and female subjects will be included. As we are interested in the association between vitamin D and premature mortality, studies that include elderly participants only (> 65) will be excluded.

Study design

It is anticipated that the main relevant studies will be observational cohort studies that provide data for vitamin D status at the point of baseline data collection and subsequent mortality. Randomised controlled trials investigating effects of vitamin D supplementation will also be included, provided a valid measure of serum vitamin D is available.

Studies which investigate the effects of vitamin D supplementation but which do not provide a measure of vitamin D, or which estimate vitamin D level based on reported dietary intake will be excluded.

Case control, cross-sectional, qualitative and case series studies will be excluded.

Outcome measures

The primary measure of interest is premature all-cause mortality, defined as < 65 yrs of age.

Secondary outcome measures that may be included in the analysis are mortality from specific causes, e.g. cardiovascular disease, stroke and cancer.

Excluded studies

All studies will be reviewed by two people independently for relevance before a decision to include or exclude is made. Disagreements will be resolved through discussion and if necessary, arbitration by a third reviewer.

Quality Assessment

All included studies will be critically appraised independently by two reviewers to identify potential sources of error, bias and confounding. Again, an attempt will be made to resolve disagreements by further discussion and if necessary via arbitration by a third reviewer. A validated critical appraisal tool will be used. It is anticipated that the eligible studies will be both observational and experimental in nature, therefore an appropriate tool will be used for each type of study.

Data extraction

The following data will be recorded in a standardised template for each of the

included studies:

- Study design
- Setting, including country, or region, and season in which vitamin D level was recorded
- Sample size
- Baseline characteristics of participants, including representativeness of the study population in comparison to , and the age and sex profile
- Results
- Declaration of strengths and weaknesses, including any competing interests

Data Synthesis

A summary statistic for effect size will be extracted for each study. Studies will then be assessed for heterogeneity via a forest plot, and for publication bias via a funnel plot. If appropriate, a meta-analysis will be performed.

A narrative synthesis of the main findings, and a narrative description of all studies, will be included in the finished review. Particular attention will be paid to the generalizability of the findings to the Scottish context.

Dissemination of results

The completed review will be submitted to a peer reviewed journal for consideration for publication. The thesis will also be used by my supervisors in NHS Health Scotland and the Glasgow Centre for Population Health, who are co-ordinating research to investigate the putative causes of the higher mortality in Scotland and the 'Scottish Effect'.

Timeframe

Nov – Jan	Finalise protocol Make contact with key people, e.g. subject librarian
Jan – March	Literature search and review Development of critical appraisal and data collection methods Complete screening process for article relevance and critical appraisal of included articles
April - June	Completion of data extraction Analysis and synthesis of data Writing up for thesis and journal publication

Submission Date: 6th August 2012

Ethical approval

No ethical approval is required for this project as it does not involve primary data collection.

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