Micronutrient deficiencies and health-related quality of life (HRQoL): the case of children with Vitamin D deficiency

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Ethical Standards Disclosure

The project was submitted to the University of Birmingham Ethical Review Committee - reference number ERN_16-0370. No ethics approval was required.

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Conflict of interest

None to declare.

Authorship

MA and EF developed the research question. All authors contributed to the development of its methods. MA and WH developed and validated the health states. MA designed the survey structure, with supervision of all other authors. WH supported with the recruitment. MA carried out the data analysis. All authors discussed the interpretation of the findings. MA wrote the first draft of the manuscript. LA, MP, WH and EF revised the manuscript and contributed significantly to its scientific content.
Abstract

Objective: To explore the extent to which micronutrient deficiencies (MNDs) affect children’s health-related quality of life (HRQoL), using Vitamin D deficiency (VDD) as a case study.

Design: Proxy valuation study to estimate the impact of VDD on the HRQoL of younger (0-4 years) and older (>4 years) children. We used the Child Health Utility 9 Dimension (CHU9D) questionnaire to estimate the HRQoL for children within six VDD related health states: ‘hypocalcaemic cardiomyopathy’, ‘hypocalcaemic seizures’, ‘active rickets’, ‘bone deformities’, ‘pain and muscle weakness’, and ‘sub-clinical VDD’.

Setting: Sampling was not restricted to any particular setting and worldwide experts were recruited.

Subjects: Respondents were paediatric bone experts recruited through network sampling.

Results: Thirty-eight experts completed the survey. The health state with the largest detrimental impact (mean score ±SE) on children’s HRQoL was hypocalcaemic cardiomyopathy (0.47 ± 0.02), followed by hypocalcaemic seizures (0.50 ± 0.02) and active rickets (0.62 ± 0.02 in young children; 0.57 ± 0.02 in older children). Asymptomatic VDD had a modest but noticeable negative impact on HRQoL, attributed mostly to tiredness in both age groups, and pain in the older paediatric population.

Conclusion: Elicitation of HRQoL from clinical experts suggests a negative impact of VDD on HRQoL, even if there is no recognisable clinical manifestation. HRQoL data from populations of patients with MNDs will inform public health policy decisions. In some settings, routine collection of HRQoL data alongside national nutrition surveys may help capture the full burden of MNDs, and prioritise resources towards effective prevention.
Introduction

Micronutrient deficiencies (MNDs) are underlying causes of disease, with impact on the quality of life, morbidity, and mortality of populations, and threatening health and wellbeing globally (1). They are a known cause of specific diseases, such as anaemia in the case of iron deficiency, and osteomalacia in the case of Vitamin D deficiency (VDD) (1), but it is the hidden burden of sub-clinical or undiagnosed pathology that turns MNDs into a public health challenge, sometimes referred to as a ‘hidden hunger’. Besides the more obvious clinical manifestations, milder MNDs cause a wide range of non-specific imbalances that are more difficult to recognise and lead to reduced resistance to infection, metabolic disorders, and impaired growth and development (1-3). The World Health Organization (WHO) warns of the potentially huge implications of MNDs in population health, which are not limited to developing countries (2). MNDs in children affect development and school attainment, and are a general reflection of a country’s inequalities (3). Difficulties in assessing the real burden of MNDs might be partly overcome with the use of health-related quality of life (HRQoL) measures, which are able to capture health status beyond the clinical symptoms, as they encompass the physical, emotional and social components of wellbeing and health.

Vitamin D is fundamental to bone mineralization and growth (4). Vitamin D status is defined through a blood test that measures the serum 25-hydroxyvitamin D (25OHD). Serum levels below 30 nmol/L are considered deficient (5). VDD is one of the commonest MNDs globally, and is widespread in children and adult populations (6). The overall prevalence of VDD in Europe has been estimated as 13% (7). In the UK, data from the national diet nutrition survey shows that 10% of the young children (4-10 years) and 26% of older children (11-18 years) had serum 25OHD below 25 nmol/L (8). Girls were found to be at higher risk than boys, with 13% of the young girls and 39% of the older girls presenting with low 25OHD (<25 nmol/L). Severe VDD in infants and children manifests as hypocalcaemic seizures (9-11), dilated cardiomyopathy (12-14) and rickets with osteomalacia (15, 16), which in turn leads to bone deformities and muscle weakness (4, 11, 17, 18). Mild or short periods of deficiency are often asymptomatic, and it is not known if this impacts on wellbeing. Symptomatic VDD in the UK, USA and Skandinavian countries...
occurs almost exclusively in dark-skinned populations from African, Caribbean and South-Asian backgrounds (Fitzgerald skin type IV-VI) (19). Although symptomatic VDD falls into a rare disease definition (incidence is below 5 in 100,000) (20), the prevalence of rickets is increasing in high income countries as population structures are changing (11, 19, 21-23), with greater proportions of populations from high risk groups (e.g. dark skin pigmentation, full-body clothing, limited sunlight exposure). The risk is aggravated by high latitude, low availability of vitamin D rich foods (4) and diets that are poor in calcium (24). The resurgence of rickets is of concern to public health and health care agencies (23, 25).

Although the clinical outcomes of VDD in children are known, there is a lack of information on the extent to which VDD affects HRQoL (26). In adults, low serum 25OHD is associated with reduced HRQoL (27-29). This lack of HRQoL data in the paediatric population may result from the difficulties of identifying patients, as: symptoms are rare (20); VDD is under-reported in clinical settings (30); and there is seasonal variation in VDD status (25). The absence of HRQoL data limits the availability of cost-utility analyses (CUAs) needed to inform public health policies (26).

This paper presents a study which aimed to estimate the HRQoL of children with VDD, through administration of a multi-attribute preference based questionnaire to clinical experts in paediatric VDD (proxies).

This study also aimed to elucidate how VDD impacts the HRQoL of children. This will help to highlight how MNDs affect population health and wellbeing, what the obstacles are for routine data collection, and offer some suggestions for how these might be overcome.

**Subjects and Methods**

Clinical experts in paediatric bone disease were approached as proxy respondents to value VDD related health states. Proxy elicitation is an established method of obtaining HRQoL information, particularly when patients cannot state their own preferences, as is the case for infants and young children, or for those suffering from incapacitating conditions. When using proxies, patient representatives such as health care professionals or informal carers (typically family members and friends), are asked to complete a validated HRQoL questionnaire, either acting as they think the patient would (31), or by providing their own perspective on the patient’s HRQoL (31, 32).
In this study, HRQoL estimates for a range of health outcomes linked to VDD were elicited for two age groups: i) 0-4 years and ii) >4 years. The use of proxies was necessary for the younger age group as infants and very young children are unable to provide self-reported HRQoL estimates. Proxies were also used for the older age group, as recruitment of a sufficient number of older children with VDD-related diseases/symptoms is challenging due to the rarity of VDD-associated diseases (9, 11, 33), and the under-reporting of VDD-related symptoms (34).

**Participants**

Experts were recruited from three professional groups: the Rickets Global Consensus Group (4); the Bone and Growth Plate Working Group of the European Society of Paediatric Endocrinology (35); and the British Paediatric and Adolescent Bone Group (36). The questionnaire was initially sent to 133 experts. Further recruitment of participants was done through a snowball sampling method whereby the initial group of experts contacted were asked to forward the survey link to any other colleague that they considered to have the relevant expertise. A further 10 experts were contacted in this way.

**Health state development**

The health state development was divided into two phases: phase 1 involved a literature review to identify the relevant health states in children with VDD; and phase 2 was an expert consultation using an iterative approach to refine the health state descriptions. The literature review that informed phase 1 has been described elsewhere and formed part of the Global Rickets Consensus statement (4). Criteria for health state selection was based on prevalence and severity. Five health states were initially described: hypocalcaemic cardiomyopathy (12-14), hypocalcaemic seizures (9-11), active rickets with skeletal deformities (15, 16, 37), pain and muscle weakness (11, 17, 18), and asymptomatic VDD. Based on the literature, the five health states were then divided by age group, using serum 25OHD below 30 nmol/L as the accepted definition of VDD (4, 5). All **five were** described for infants and young children up to 4 years old, but only active rickets, skeletal deformities, pain and muscle weakness and asymptomatic VDD were used for older children (aged 5 -18 years). This was because VDD-related hypocalcaemic
cardiomyopathy occurs almost always in infants (12-14, 38), and hypocalcaemic seizures are rare in children over 5 years (9, 38). In phase 2, the health state description was presented to two paediatric bone experts. Through an iterative process involving 3 rounds of consultation, the health state descriptions were adjusted to align with the preferred wording of clinical experts. This consultation led to the inclusion of a sixth health state in which children continue to suffer from residual leg deformities after having been treated for rickets (11, 15, 39) and require long-term vitamin D supplementation. Although this health state was not identified in phase 1, the experts attributed significant clinical relevance to it, and it was therefore included in the final set of health states (Figure 1).

Health State Valuation

Valuation of the health states was undertaken using a proxy version of the Children’s Health Utility 9 Dimension (CHU9D) instrument, a multi-attribute preference based questionnaire. Multi-attribute preference based questionnaires are health state classification systems that allow the indirect estimation of health state utility values, based on the public’s preferences for a given health state. Utilities quantify HRQoL through preference scores on a generic scale anchored between 0 (dead) and 1 (perfect health), where values below 0 represent health states that are deemed worse than dead (28, 29).

The CHU9D questionnaire has been validated in the 5-18 year age group (40-44). A separate version of the questionnaire is available for children under 5 years (45). The CHU9D is a questionnaire with 9 dimensions: worried, sad, pain, tired, annoyed, school work/homework, sleep, daily routine, and activities. Each dimension has 5 levels (e.g. “Last night the child had no problems, few problems, some problems, many problems sleeping”, or “Last night the child couldn’t sleep at all”) (46). For infants and young children, to whom dimensions such as school work and ‘feeling annoyed’ do not apply, a specific version was used which provides a short explanation of how questions should be interpreted. For example, respondents were asked to replace school work by learning activities that would apply to the younger age groups. The clinical experts were asked to value each VDD health state using the CHU9D dimensions, which enabled a utility value to be applied to each health state, using a pre-existing value set developed for the CHU9D (46).
Structure of the Survey

The online survey was divided into three separate sections: infants and younger children (0-4 years); older children (5-18 years); and general questions regarding the respondent’s professional practice.

All respondents were asked to assess all health states using two different methods, for both age groups. First, the respondents were asked to rank the health states according to their severity, or detrimental impact upon HRQoL, with number 1 corresponding to the least severe health state. Second, the respondents were asked to complete the CHU9D questionnaire considering a hypothetical patient who visited their clinic on that day. Respondents were asked to answer, based on their clinical experience, how they thought the patient would feel/perform in that given health state. The final section of the survey asked respondents about their area of expertise, their country of practice and how many cases of rickets they had seen in the last two years.

Analyses

The responses to the CHU9D questionnaire were converted into utility values by applying an established algorithm (46) using Stata 13 software (StataCorp L; College Station, TX, USA). HRQoL estimates are presented as mean utility values, with the corresponding standard error (SE) and 95% Confidence Intervals (95% CI).

Results

Of the 143 experts contacted, 38 (26.6%) completed and returned the questionnaire. Table 1 presents the respondents’ areas of expertise and countries of practice. Experts from 18 different countries responded, the majority of whom were based in the UK (23.7%) and France (13.2%), and 34% in non-European countries. Most experts were either paediatric endocrinologists (39.5%) or paediatricians with a special interest in endocrinology or bone disease (31.6%). Most respondents (N= 35, 92%) had treated at least one case of rickets in the last 2 years. The total number of cases seen per expert ranged from 1 to 30.
A. Ranking scores

In the infants and young children group (0-4y), hypocalcaemic cardiomyopathy was ranked as the most severe health state followed by hypocalcaemic seizures, active rickets, leg deformities, pain and muscle weakness and the asymptomatic health state (Figure 2). For older children (5-18y), active rickets was considered to be the most severe health state, followed by leg deformities, pain and muscle weakness, and asymptomatic VDD (Figure 3). One respondent ranked asymptomatic VDD as the most severe. This respondent’s data has been included in figure 3 for completeness, but in this instance, it is assumed the question was misunderstood.

B. Utility scores

The CHU9D summary results are presented in Table 2. All health states resulted in some disutility, with hypocalcaemic cardiomyopathy (0.465, 95% CI [0.425; 0.505]), and hypocalcaemic seizures (0.495, 95% CI [0.458; 0.531]) resulting in the lowest utility scores. Health states that were assessed in both age groups (active rickets, leg deformities, pain and muscle weakness, and asymptomatic VDD) had similar utility scores. In the younger children group, the estimates of utility scores for hypocalcaemic cardiomyopathy (0.465, 95% CI [0.425; 0.505]) and hypocalcaemic seizures (0.495, 95% CI [0.458; 0.532]) were similar, with overlapping confidence intervals. This was also the case for active rickets, and pain and muscle weakness in both age groups.

For both age groups, the asymptomatic health state was associated with some disutility and ‘feeling tired’ was the main cause of such disutility. In young children, other factors contributing to lower utility scores in the sub-clinical health state were ‘lower ability to join in daily activities’, ‘feeling annoyed’ and ‘feeling pain’, while in the older children group these were ‘feeling annoyed’ and ‘pain’.

Discussion

This is the first study to report utility values for VDD health states in children. Our preliminary results are indicative of the detrimental impact of VDD upon HRQoL and its potential to contribute to the burden of disease that has not yet been measured. Given the
high prevalence of VDD, even if mainly in its asymptomatic or undiagnosed form, we have highlighted the importance of intensifying research in this field.

Evidence on the utility of VDD related health states might contribute to more efficient decisions when it comes to allocating resources to the prevention and treatment of VDD. Utilities are used to calculate Quality-Adjusted Life Years (QALYs). QALYs are a composite outcome that combines HRQoL with length of life, and are used as the measure of benefit in cost-utility analyses. Health benefit measured by QALYs is the preferred format of information for health care policy makers in many countries, including the UK (28, 30-33).

This study highlights the importance of considering the population impact of MNDs upon HRQoL in children, provides novel evidence of the impact of VDD on children’s HRQoL, and opens up an opportunity to reflect on the methods used for collecting HRQoL data for paediatric populations with MNDs. The results show coherence with the severity of health states reported in the literature, and the narrow confidence intervals of the estimates suggest that there is agreement among experts on the impact of VDD on children’s HRQoL. The ranking exercise was introduced as a warm-up question to familiarise respondents with the health states. As expected, there was better agreement between the results of the ranking exercise and the CHU9D utility scores for the health states ranked in the extremes, i.e., the most and least severe health states: hypocalcaemic seizures, cardiomyopathy, and asymptomatic VDD. While the most and least severe health state can be easily placed in the extremes of the scale, variation is expected in the mid-severe health states, where variation in the respondents’ perception of severity, and within patient variations are more likely to occur. Using the CHU9D questionnaire reduced this variation, as the health states are broken down by physical, emotional and social dimensions, which helps to value health states more objectively.

VDD is a very common MND but symptomatic complications that lead to clinical presentation or hospital admission are rare. Therefore, hidden or undiagnosed disease is widespread in the population, with 25% of a low-risk population having osteomalacia on bone biopsy (47), and two thirds of family members of infants with rickets having biochemical evidence of osteomalacia (14).
Our study found that sub-clinical health states of VDD might lead to reduced HRQoL in children, mainly due to fatigue. Although the literature is sparse, evidence from primary care units shows a link between low levels of vitamin D and fatigue in adults. A study conducted in a health centre in Oslo, Norway, found that 58% of the patients presenting with musculoskeletal pain, fatigue and headache had insufficient levels of Vitamin D (<50 nmol/L) (48). A different study in the USA found that 77.2% of patients with fatigue symptoms had 25(OH)D levels < 70 nmol/L, and their symptoms improved after treatment with Vitamin D (49). Further research should explore if the same effect occurs in children. If this is the case, improving children’s Vitamin D status VDD might have benefits beyond bone and muscle health, including general wellbeing and school attainment.

In this study, clinical experts valued VDD-related health states relevant to the paediatric population. The health states associated with lower HRQoL in younger children were hypocalcaemic cardiomyopathy, hypocalcaemic seizures, and active rickets. In older children, active rickets, and pain and muscle weakness resulted in the lowest HRQoL. Low serum 25OHD alone, described as the asymptomatic health state, was valued as causing a small but significant decrement in HRQoL in both age groups.

The health states were developed using robust methodology, based on the systematic evidence-based literature review that informed the Rickets Global Consensus Recommendations (4). Given the many barriers to the collection of HRQoL data in children (50), our study offers valuable insight from a pool of informed respondents. The results show that most respondents have experience in treating symptomatic VDD, which is a rare area of expertise amongst paediatricians. Such rare disease expertise might explain the moderate response rate (27%), which is nonetheless comparable to other studies (37, 51). Moreover, recruiting clinical experts is a critical step in health research, and low participation rates have been reported in the literature (31, 37, 51-54). Barriers to participation are many, including lack of time or capacity, and lack of familiarity or understanding the research objectives (52, 53). Network sampling has the limitation of allowing self-selection, which leads to biased estimates given by experts that share similar views, leaving those that would disagree outside of the recruited sample. In order to overcome this, efforts were made to reach more than one professional group, and within each group, all individuals were invited to participate. The respondents are therefore
experts with similar professional backgrounds, rather than professionals with similar points of view.

The use of proxy data in patient groups that could potentially provide self-reported estimates (namely the older children group) might be seen as a limitation since self-reported HRQoL is the gold-standard method, and the evidence suggests that there can be disagreements between patient and proxy reports. Morrow et al. compared children’s, parents’ and doctors’ perceptions of HRQoL associated with chronic paediatric conditions and found lower agreement in the subjective components, such as emotional well-being (55). Similar findings have been reported for adult populations (31). Nonetheless, the literature on patient versus proxy utility values is inconsistent, with some studies reporting no difference between patient and proxy (56), as well as under- (57) and over-estimation (58) of HRQoL by the proxy. While we acknowledge that self-reported preferences from children with VDD would potentially better reflect utility scores for VDD health states, collecting such data is impractical. Children younger than 5 years old are not able to self-report preferences for health states. Although methodologically sound, collecting utility data from older children with various VDD health states is impractical in a research context, since clinical presentation with symptomatic VDD in this age group is extremely rare despite biochemical abnormalities (11, 33, 59). Since parents have daily contact with their children, they are a commonly used and trusted source of health state utility values in paediatric populations. Nevertheless, in our study, recruiting parents of children with VDD was not a viable option due the rarity of symptomatic VDD. To recruit a satisfactory number of parents of children experiencing each of the health states would have been impractical.

In terms of future collection of MND-associated HRQoL, in countries such as the UK, it may be feasible to collect these data alongside the National Diet and Nutrition Survey, a biennial routine survey undertaken to monitor the nutritional status of the population. This could offer an efficient way of collecting cross-sectional data on HRQoL, and would open numerous possibilities to study the dynamics between diets, nutritional status, and HRQoL at a population level. For cases of symptomatic VDD identified in a clinical setting, collection of qualitative information during follow-up would help understand how VDD
affects individuals in the long term, including delayed bone and muscle development, quality of life and productivity.

The results of this study call for more targeted research into the impact of MNDs upon the HRQoL of populations to generate better data to inform public health policies, and therefore more efficient use of scarce public resources.

**Conclusion**

By eliciting utility values from health professionals, this study translates clinical knowledge and expertise into information that can be used to support policy makers identifying cost-effective strategies for tackling VDD. The research presented will in turn stimulate and support future studies to collect HRQoL information from MND populations, using outcome measures that generate utility values. At a time of global austerity, it is essential to ensure efficient use of scarce health care resources, as well as adequate estimates of burden of disease.
References

38. Högl er W. Complications of vitamin D deficiency from the foetus to the infant: One cause, one prevention, but who's responsibility? Best Practice & Research Clinical Endocrinology & Metabolism. 2015;29(3):385-98.
Figures legends

Figure 1 – Final Health State description
Figure 2 – Results from ranking exercise for young children (0-4 years). 0 corresponds to the least severe condition and 6 to the most severe.
Figure 3 - Results from ranking exercise for older children (>5 years old). 0 corresponds to the least severe condition and 4 to the most severe
**Table 1 - Area of expertise and country of practice**

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<thead>
<tr>
<th>Specialty</th>
<th>N (Total=38)</th>
<th>%</th>
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<tr>
<td>Paediatric endocrinologist</td>
<td>15</td>
<td>39.5</td>
</tr>
<tr>
<td>Metabolic bone specialist</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td>Paediatrician (non-specified specialty)</td>
<td>12</td>
<td>31.6</td>
</tr>
<tr>
<td>Paediatric rheumatologist</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>13.1</td>
</tr>
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<table>
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<th>Country of practice</th>
<th>N (Total=38)</th>
<th>%</th>
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<tr>
<td>UK</td>
<td>9</td>
<td>23.70%</td>
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<td>France</td>
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<td>13.20%</td>
</tr>
<tr>
<td>Sweden</td>
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<td>7.90%</td>
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<td>Poland</td>
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<tr>
<td>The Netherlands</td>
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<td>5.30%</td>
</tr>
<tr>
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<tr>
<td>Other</td>
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Table 2 - Health state utility values for young children and older children with low 25OHD concentrations

<table>
<thead>
<tr>
<th>Health state</th>
<th>Mean (SE)</th>
<th>[95% CI]</th>
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<tbody>
<tr>
<td><strong>Infants and young children (0-4 years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcaemic Cardiomyopathy</td>
<td>0.465 0.020</td>
<td>[0.425; 0.505]</td>
</tr>
<tr>
<td>Hypocalcaemic seizures</td>
<td>0.495 0.018</td>
<td>[0.458; 0.532]</td>
</tr>
<tr>
<td>Pain and muscle weakness, delay in motor milestones and poor growth</td>
<td>0.612 0.022</td>
<td>[0.566; 0.657]</td>
</tr>
<tr>
<td>Active rickets</td>
<td>0.621 0.018</td>
<td>[0.586; 0.657]</td>
</tr>
<tr>
<td>Leg deformities</td>
<td>0.758 0.019</td>
<td>[0.720; 0.796]</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.955 0.014</td>
<td>[0.927; 0.983]</td>
</tr>
<tr>
<td><strong>Older children (&gt;4 years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active rickets</td>
<td>0.567 0.021</td>
<td>[0.524; 0.610]</td>
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<tr>
<td>Pain and muscle weakness, delay in motor milestones and poor growth</td>
<td>0.608 0.020</td>
<td>[0.567; 0.648]</td>
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<tr>
<td>Leg deformities</td>
<td>0.708 0.020</td>
<td>[0.668; 0.748]</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.946 0.012</td>
<td>[0.921; 0.970]</td>
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</table>
Health State A
The patient is vitamin D deficient (25OHD <30nmol/L). The child presents with hypocalcaemic cardiomyopathy. The condition requires hospital care, including ventilation and inotropic support.

Health State B
The patient is vitamin D deficient (25OHD <30nmol/L). The child presents with hypocalcaemic seizures and requires hospitalisation.

Health State C
The patient is vitamin D deficient (25OHD <30nmol/L). The child presents with overt rickets, with skeletal abnormalities such as bowed legs, swollen ankles and deformed chest.

Health State D
The child presents with leg deformities following active rickets (rickets healed in deformity). If not continuously supplemented with vitamin D for life, the child may require surgery to correct deformities, and may develop active rickets again.

Health State E
The patient is vitamin D deficient (25OHD <30nmol/L). The child presents with pain and muscle weakness and may show signs of delay in motor milestones and poor growth.

Health State F
The patient is vitamin D deficient, confirmed by serum concentration of (25OHD <30nmol/L). The child may be in a pre-rickets state but nonetheless, the child is asymptomatic.
Figure 2 - Results from ranking exercise for young children (0-4 years). 0 corresponds to the least severe condition and 6 to the most severe.

Figure 3 - Results from ranking exercise for older children (5-18 years old). 0 corresponds to the least severe condition and 4 to the most severe.