1 **The economic case for prevention of population vitamin D**

2 **deficiency: a modelling study using data from England and Wales**

3 Aguiar, M[1,2], Andronis L[1,3], Pallan M[1], Högler W[4,5], Frew E[1]

4

5 [1]Institute of Applied Health Research, University of Birmingham, Birmingham, B15 2TT,

6 UK.

7 [2]Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences,

8 University of British Columbia, BC, Vancouver, V6T 1Z3, Canada

9 [3]Population, Evidence and Technologies, Division of Health Sciences, University of

10 Warwick, Coventry, CV4 7AL

11 [4]Department of Paediatrics and Adolescent Medicine, Faculty of Medicine, Johannes Kepler

12 University, Linz, A-4040, Austria

13 [5]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15

14 2TT, UK

15

18 **Corresponding author**: Dr Emma Frew, Institute of Applied Health Research, University of

19 Birmingham, Birmingham, B15 2TT. Email: e.frew@bham.ac.uk; Tel: +44(0)121 414 3199.

20 **Word count:** 3,417

21 **Number of figures:** 2

22 **Number of tables:** 3

23 **Supplementary material data submitted:** Yes

24 **Running title:** Cost-effectiveness of preventing population VDD

25 **Abstract**

26

27 **Background:** Vitamin D deficiency (VDD) affects the health and wellbeing of millions

28 worldwide. In high latitude countries such as the United Kigdom (UK), severe complications

29 disproportionally affect ethnic minority groups.

30 **Objective:** To develop a decision-analytic model to estimate the cost-effectiveness of

31 population strategies to prevent VDD.

32 **Methods**: An individual-level simulation model was used to compare: (I) wheat flour

33 fortification; (II) supplementation of at-risk groups; and (III) combined flour fortification and

34 supplementation; with (IV) a 'no additional intervention' scenario, reflecting the current

35 Vitamin D policy in the UK. We simulated the whole population over 90 years. Data from

36 national nutrition surveys were used to estimate the risk of deficiency under the alternative

37 scenarios. Costs incurred by the health care sector, the government, local authorities, and the

38 general public were considered. Results were expressed as total cost and effect of each strategy,

39 and as the cost per 'prevented case of VDD' and the 'cost per Quality Adjusted Life Year

40 (QALY)'.

41 **Results**: Wheat flour fortification was cost-saving as its costs were more than offset by the cost-

42 savings from preventing VDD. The combination of supplementation and fortification was cost-

43 effective (£9.5 per QALY gained). The model estimated that wheat flour fortification alone

44 would result in 25% fewer cases of VDD, while the combined strategy would reduce the number

45 of cases by a further 8%.

46 **Conclusion:** There is a strong economic case for fortifying wheat flour with Vitamin D, alone

47 or in combination with targeted vitamin D3 supplementation.

48

Introduction

Vitamin D helps to maintain adequate levels of calcium and phosphorus in the body, playing a fundamental role in bone and muscle health (1). The main source of Vitamin D is sunlight exposure and many behavioural, cultural or environmental factors increase the risk of VDD by limiting the skin's direct exposure to sunlight. Risk factors for VDD include, for example, sun screen use, air pollution, indoors lifestyles, full body clothing, and living in high latitude settings (2,3). People with dark pigmented skin who live in setting with limited sunlight, such as high latitude countries are also at a higher risk for VDD, as well as older adults, particularly if institutionalised. VDD can lead to poor health and its symptoms manifest as osteomalacia, bone pain, muscle weakness and consequent increased risk of falls. In children, severe VDD additionally causes hypocalcaemia (low levels of calcium in the blood), which is associated with seizures, tetany and heart failure (4,5), and rickets with osteomalacic leg bowing, muscle weakness and delayed infant development. Morbidity from VDD is predominantly found in individuals from Black and Asian Minority Ethnic (BAME) groups living in high-latitude countries, including in the UK (6,7), the US (8), Canada (9), Scandinavian countries (10–13) and Australia (8,14). Nonetheless, VDD is common in many populations across the world, regardless of ethnicity.

In response, most countries have adopted policies to increase the populations' intake of vitamin D, which generally consist of a combination of supplementation and food fortification strategies (15). In the UK, multivitamin supplements containing vitamin D are recommended to all infants and children up to the age of four, as well as to pregnant women and breastfeeding mothers (16). These vitamins are provided free-of-charge to those in low-income households. In addition, infant formulas and spreadable fats are mandatorily fortified, while other foods including breakfast cereals and milk substitutes are voluntarily fortified. While both supplements and fortified foods are important sources of vitamin D for the UK

74   population, evidence suggests supplementation polices are not working (7,17) and the mean

75   daily vitamin D intake is still below the Reference Nutritional Intake (RNI) of 400 IU per day

76   (2,18). Therefore, rickets and hypocalcemic complications remain a serious health issue and

77   cause of death in infants, particularly in the BAME group (4,7,19,20). Evidence shows that

78   vitamin D status, which is measured through the blood concentration of a Vitamin D

79   metabolite, the 25-hydroxyvitamin D [25(OH)D], is suboptimal in 13% of the European

80   population (21). In the UK population, 20% of adults and 16% of children aged between 11

81   and 18 years are estimated to be VDD (2), with the BAME group being, by far, the most

82   affected (10,12,22–25).

83   So far, the economic evidence needed to inform and underpin VDD prevention policies has

84   been limited (26). To the best of the authors' knowledge', there is no evidence on the cost-

85   effectiveness of preventing population VDD through food fortification or a combination of

86   food fortification and supplementation, even though the latter is the approach taken in most

87   countries (15). This study estimates the cost-effectiveness of preventing VDD using the

88   population of England and Wales as a simulated cohort and compares the strategies of

89   supplementation of at-risk groups, wheat flour fortification, and a combination of the two

90   approaches.

91

92   **Methods**

93   An individual-level state-transition model was developed to compare four different strategies

94   to prevent population VDD. A state transition model was chosen to allow recurrence of VDD

95   over the life course, and individual-level simulation was used to make the most efficient use

96   of available data on risk heterogeneity for VDD in the population, as well as to account for

97   individual pathways across the model's time horizon (27,28). The model used a one-year

98   cycle length, and both costs and benefits were discounted at 3.5% per year, as recommended

99   by the UK National Institute for Health and Care Excellence (NICE) (29). The base case

100   analysis was done from a societal perspective and results reported using incremental cost

101   effectiveness ratios (ICER) in the form of cost per additional quality-adjusted life year

102   (QALY) gained, and cost per prevented case of VDD. The model was built in TreeAge Pro

103   2016 software, and followed modelling (28,30) and reporting (31) guidelines for good

104   practice.

105   The model comprised three main health states (**Figure 1**). These health states were mutually

106   exclusive and represent clinically relevant stages:

107   1) <u>Vitamin D deficient (VDD)</u>: all children with serum 25(OH)D concentrations below

108   30nmol/L (3) and adults with serum 25(OH)D below 50 nmol/L (32).

109   2) <u>Vitamin D sufficient (VDS)</u>: all children with serum 25(OH)D concentrations above

110   30nmol/L (3) and adults with serum 25(OH)D above 50 nmol/L (32).

111   3) <u>Dead</u>: based on all-cause mortality and naturally treated as an absorbing state.

112

113   **[Figure 1]**

114

115   The majority of the VDD population were assumed to be asymptomatic. Within the model,

116   asymptomatic individuals followed a pathway with the possibility of remaining deficient or

117   becoming sufficient over time. For the deficient population who become symptomatic,

118   children were assigned a risk of developing rickets and hypocalcemic complications, and

119   adults a risk of developing osteomalacia. Younger adults aged between 19-64 years old who

120   acquire osteomalacia suffer from diffuse pain and muscle weakness. Older adults with

121   osteomalacia had a modest increased risk of falls due to pain and muscle weakness. The full

122   model structure depicting the clinical pathways for children and adults with symptomatic

123   VDD can be found in the supplementary material (Figure S1 and Figure S2).

124   The starting cohort within the model was simulated based on the population of England and

125   Wales, according to its age, sex and ethnicity distributions (33). The following four

126   alternative strategies were compared: (I) wheat flour fortification at 400IU of Vitamin D per

127   100 g of wheat flour; (II) free supplementation to all at-risk groups; (III) a combination of

128   flour fortification and supplementation; and (IV) no additional intervention, i.e. maintaining

129   the current fortification and supplementation policy of providing supplements to young

130   children, pregnant women and breastfeeding mothers within low-income households, and

131   fortifying certain food groups. Wheat flour was chosen as the most appropriate food for

132   fortification since, contrary to milk and spreadable fats, flour is a staple food across multiple

133   ethnic groups, including Asian, African, Caribbean, and white ethnic groups, and therefore

134   will potentially reach multiple at-risk groups. Evidence from Scandinavian countries shows

135   that milk supplementation is not as effective in reaching ethnic minority groups as it is in

136   reaching white ethnic groups (15). Regarding safety, a UK study that compared vitamin D

137   fortification of milk, flour and a combination of both showed that flour fortification alone

138   presented the lowest risk of toxicity in the population (34). Wheat flour is already fortified in

139   the UK, and addition of vitamin D to the mix of added nutrients is likely to carry lower

140   implementation barriers than targeting an industry that has no fortification infrastructure, in

141   place, such as milk in the UK. The baseline risk of VDD was estimated using individual-level

142   intake data reported from the National Diet and Nutrition Survey (NDNS) (18,35). The intake

143   of vitamin D included all food sources (natural and fortified foods, including voluntarily

144   fortified). Differences in intake by age group and sex were considered.

145   The effectiveness of wheat flour fortification in reducing the risk of being VDD by sex was

146   derived from Allen et al.'s nutrition model (34,36). Ethnicity specific effects were not

147   available and therefore the same effect was assumed for white and BAME populations. The

148   full list of the transition probabilities used in the model for the current UK policy and wheat

149   flour fortification is presented in the supplementary material (Table S1.A. and Table S1.B.).

150   The effect of the supplementation programme was based on data provided by a local

151   government organization in London, UK (37), which recorded the uptake of free vitamin D

152   supplements using an electronic card system. In this Local Authority, all children up to 4

153   years old, pregnant women and breastfeeding mothers were eligible to receive free Vitamin D

154   supplements. In our model, supplements were provided to all sub-populations at risk of

155   symptomatic VDD including all infants and young children up to 18 years old; individuals of

156   all ages from BAME backgrounds; and all individuals aged over 65 years. In the absence of

157   data on the uptake of supplements by adults and older children (>4 years old), we assumed the

158   same uptakes in older and younger children to that of children <4 years, and the adult uptake

159   to be the same as that of pregnant and breastfeeding women. The model assumed a

160   supplement dosage of 400IU per day for all groups except for the elderly, who received

161   800IU per day as per the recommended minimum dose to prevent falls (38). The effectiveness

162   of the combined scenario (wheat flour fortification plus supplementation of at-risk groups)

163   was estimated as the additive effectiveness of each strategy alone.

164   **Outcomes**

165   Preventing VDD in the population reduces the risk of poor bone and muscle health. The

166   outcome unit used for the cost-effectiveness analysis was the number of cases of VDD

167   prevented. For the cost-utility analysis, the health-related quality of life (HRQoL) for a given

168   health state was combined with the time spent in that health state to formulate QALYs. The

169   preference-based quality of life values (i.e. utilities) applied to estimate QALYs were sourced

170   from two HRQoL studies, published elsewhere (39), one focusing on VDD in children, and

171   the other in adults (supplementary material, table S2).

172

173 **Costs**

174 Cost data were derived from multiple sources (supplementary material, table S3). For the

175 wheat flour fortification strategy, the price of dried vitamin D was obtained from a UK

176 commercial flour supplier of the food industry (LFI (UK) Ltd). The costs of re-labelling

177 packages, used in a sensitivity analysis, and the public sector costs of enforcing mandatory

178 fortification were sourced from the Food Standards Agency's study of wheat flour

179 fortification with folic acid (40). The cost structure of the supplementation programme was

180 based on the Local Authority's supplementation programme (37), which was pharmacy-led. It

181 was assumed that supplements would be supplied through community pharmacies, which

182 would receive an initial financial incentive for participating in the programme and

183 reimbursements for the cost of the supplements dispensed. An additional incentive would be

184 provided for each supplement dispensed to encourage sustained adherence to the programme.

185 **Uncertainty and sensitivity analyses**

186 Several sensitivity analyses were conducted to determine how sensitive the model results

187 were to the assumptions made (Table 1). First, the time horizon was varied to 5 and 10 years.

188 Second, the discount rate for both costs and benefits was set to 1.5%. Third, the perspective

189 was altered to include only public sector costs, therefore eliminating all private costs borne by

190 the food industry. Fourth, following the Food Stardards Agency report on the cost of

191 fortifying flour with folic acid in the UK (40), the model included a conservative estimate for

192 the food industry costs of relabelling flour packages, and all products containing flour, such as

193 cakes and biscuits. Fifth, the model assumed no disutility from asymptomatic VDD. Sixth, the

194 starting cohort was altered to include a higher proportion of BAME individuals, reflecting the

195 population mix of many large UK cities (33). Finally, a probabilistic sensitivity analysis was

196 conducted based on 10,000 iterations of a Monte Carlo simulation, using the model parameter

197 distributions listed in the supplementary material (Tables S4-S11).

198

199   **[Table 1]**

200

201 **Results**

202 The model base case analysis showed that wheat flour fortification was cost-saving, which

203 means that it led to fewer costs and more benefits when compared to the current national policy

204 in England and Wales, and is therefore described as dominant (Table 2). All other strategies

205 were found to be superior to the current national policy in terms of cases of VDD prevented.

206 The model estimated that if the current VDD policy is kept in place, there will be almost 40

207 million new cases of VDD – asymptomatic and symptomatic - over the next 90 years.

208 Introducing wheat flour fortification would result in a 25% reduction in this number, and if that

209 is combined with an additional supplementation programme then a further 8% would be

210 prevented (33% in total). The model estimated that wheat flour fortification would lead to an

211 increased expenditure of £0.12 per person per year based on consumption estimates that include

212 common flour based products such as cakes and biscuits (41). The model found the strategy of

213 flour fortification to be cost-saving, saving approximately £65 million over a 90-year time

214 horizon. If food fortification is combined with supplementation, then this would lead to an

215 additional cost of nearly £2 per case of VDD prevented but more cases of VDD would be

216 prevented when compared to fortification alone.

217

218   **[Table 2]**

219

220   The analysis showed that wheat flour fortification at 400IU per 100g of flour combined with

221   targeted supplementation at 400IU for children up to 18 years old and all individuals from

222   BAME backgrounds and 800IU for all individuals older than 65 years old is cost-effective. The

223   intervention costs on average £0·38 per person across the whole population (total costs over the

224   90 years modelled is 250 million) and leads to an average gain of 0·04 QALYs, resulting in an

225   ICER of £9·50 per QALY gained (table 3). Under commonly applied UK thresholds of

226   willingness to pay per QALY, this represents a highly cost-effective use of resources.

227   **[Table 3]**

228

229   The sensitivity analyses showed the model results were not sensitive to the majority of the

230   assumptions made. Consistently, with each subsequent sensitivity analysis, the model showed

231   the flour fortification strategy to be dominant and the combined strategy to impose a small cost

232   but to be highly cost-effective. Evidence from the literature suggests that asymptomatic VDD

233   – (serum concentrations of 25(OH)D levels below the deficiency threshold, but no overt

234   symptoms), if coexisting with limited dietary calcium, are regarded as a pre-clinical health risk

235   state, with diffuse pain (1), muscle weakness and fatigue (42), and thus likely to impact on

236   quality of life. In the base case analysis, a detrimental impact on HRQoL was assumed based

237   on an expert elicitation study (39). We tested this assumption in a sensitivity analysis and noted

238   that when it is assumed that the asymptomatic VDD health state results in the same quality of

239   life as being vitamin D sufficient, then the combined strategy has no additional benefit

240   (supplementation material, appendix 4).

241   Finally, the probabilistic sensitivity analysis (**Figure 2**) showed that for willingness to pay

242   values of up to £200 per QALY, wheat flour fortification is the recommended option. For values

243   above £200 per QALY, a combination of wheat flour fortification and supplementation of all-

244   at risk groups is the optimal strategy.

245

246 **[Figure 2]**
247

248

249 **Discussion**

250 Our model found that implementing strategies to prevent VDD is likely to be cost-effective and

251 wheat flour fortification to be cost-saving as compared to the current policy in England and

252 Wales. The costs of implementing and running the fortification scheme were more than

253 compensated for by the health care savings from preventing more cases of VDD. Alternatively,

254 the combined strategy of adding Vitamin D to wheat flour and extending the coverage of

255 supplementation to all at-risk groups would be highly cost-effective strategy. Therefore, for an

256 additional cost, the combined strategy prevents more cases of VDD when compared to

257 fortification alone and under conventional decision-making rules(43), this additional cost would

258 be regarded as a highly cost-effective use of public resources.

259

260 These results of our study are in line with published economic evaluations of food fortification

261 programmes for other micronutrients, such as folic acid (44–46), which have found food

262 fortification to be cost-saving, in pre- and post-implementation studies. The economic

263 advantage of food fortification lies in the wide-coverage and shared costs across the private

264 sector, consumers and the government. Food fortification has the potential to target hard-to-

265 reach populations, overcoming some of the problems with low uptake of supplementation

266 programmes. Moreover, fortification has a far lower burden on the health care budget than

267 supplementation alternatives, as most costs of the food fortification programme are borne by

268 the food industry, and passed on to the consumer. However, a combined strategy offers both a

269 nutritional safety net to the population by fortifying the food chain, and a targeted

270 supplementation scheme to those who are most in need.

271

272 We have included children, BAME groups and individuals aged over 65 years old in the at-risk

273 group of the population. Even though most severe cases of VDD have been reported in BAME

274 mothers and their new-borns, overall pregnant women benefit from adequate levels of 25OHD.

275 Most vitamin D supplementation policies around the world already target pregnant women and

276 infants. When considering new public health approaches to reach at-risk and vulnerable groups,

277 pregnant women should continue to be a target group for the strategy of supplementation.

278

279 The analysis presented here is based on hypothetical scenarios with conservative assumptions

280 applied to increase confidence in the results. For example, potential savings in primary care

281 associated with consultation of general practitioners and testing were not included, such as the

282 economic burden from routine 25(OH)D testing. In children alone, these costs were estimated

283 to be £1·7 million (at 2014 prices) (47). As new and more expensive diagnostic tests are

284 introduced, the economic burden is likely to increase. Furthermore, conservative estimates

285 regarding the modelling of VDD-related falls in the elderly were also applied, based on a recent

286 economic evaluation study by Poole et al (2015) (48).

287

288 We have focused on the benefits of vitamin D to bone and muscle health. The emerging

289 evidence of potential wider benefits of maintaining a healthy vitamin D status such as

290 prevention of cancer and cardiovascular disease (49,50), acute respiratory infections, (51) and

291 other illnesses (52), suggests that the impact of public health measures to tackle vitamin D

292 deficiency might be even stronger than that reported in this study. A recent meta-analysis using

293 individual patient data from over 10,000 individuals found that vitamin D supplements reduced

294   the risk of acute respiratory infections, such as colds and the flu, which have a tremendous

295   burden in population health and health systems (51). As more robust evidence on non-

296   musculoskeletal effects of vitamin D from interventional studies become available, there is

297   potential for future models to incorporate these additional benefits. If the same public health

298   measures compared in our model are able to prevent other diseases, the cost-effectiveness

299   results will be even more favourable that the ones we present here.

300   One of the strengths of the model is that it was informed by direct communication with

301   stakeholders, including clinical experts, local UK public health organisations, established

302   researchers with experience in economic evaluation of micronutrient interventions, and expert

303   investigators in the economics of food fortification. Moreover, this is the first model to compare

304   supplementation and food fortification with vitamin D independently, as well as the

305   combination of both in the same analysis, which is a more meaningful way of representing the

306   relevant alternatives for policy makers to consider. Our findings were robust when tested under

307   a number of deterministic sensitivity analyses and a probabilistic sensitivity analysis.

308

309   The model has some limitations. Data on the costs and uptake of the supplementation

310   programme were sourced from a Local Authority, and were extrapolated to a nation-wide

311   scenario. Regarding the costs, for example, purchases at the national level might achieve

312   economies of scale and result in lower costs. To account for this uncertainty, each relevant

313   model input (eg. cost estimates) was assigned a wide distribution within the probabilistic

314   sensitivity analysis. There was a lack of data on the uptake of supplements by ethnic groups

315   who have different risk profiles for developing VDD. In the absence of uptake data by ethnic

316   group, equivalent levels were applied to all ethnic groups. Furthermore, the cost and

317   effectiveness of the combined strategy was assumed to be the sum of the costs and effectiveness

318   of the flour fortification and supplementation strategies combined. In reality, if implemented

319   simultaneously, interactions between the two strategies are likely, although it is unknown in

320   which direction. Finally, the model only included the health-related benefits from preventing

321   VDD and any other benefits beyond health were not included. Economic evaluation requires

322   that the relevant benefits and costs of each of the policy alternatives are quantifiable. This is the

323   greatest challenge when applying standard economic evaluation methods to the prevention of

324   micronutrient deficiencies. The benefits from reducing the prevalence of vitamin and mineral

325   deficiencies are wide but hard to measure (53). Nutrition, including vitamin D status, impacts

326   human development from conception until the later stages of life (54–56). Moreover, poor

327   nutrition affects socioeconomically disadvantaged groups of the population, and tackling it

328   would have a wider economic benefit by addressing health and social inequalities (57). For

329   example, there would be a clear social benefit from reducing the prevalence of VDD in minority

330   ethnic groups, as it would reduce any stigma associated with rickets in children (58).

331

332   The effectiveness of any fortification programme depends on a number of programme design

333   choices, for example, the food chosen needs to be consumed by the targeted population, and

334   the price increase of the final product should be kept low, so that no access barriers based on

335   income are not created (53,59). These features of a programme are particularly important in the

336   context of VDD since BAME groups are at a higher risk. Other studies have highlighted that

337   there is a need to collect data on the diet and nutritional status of BAME populations in the UK

338   (60). We corroborate such needs. To date, nutritional data from the NDNS have not been

339   reported by ethnic group. Doing so would facilitate implementation of food fortification

340   programmes, the effectiveness of which could be monitored using the existing structures, as

341   done in other countries such as Finland (21). Fortifying flour would ensure that population

342   serum 25(OH)D concentrations are raised to safe levels with supplementation used to target

343   subgroups that the fortification programme may not reach effectively.

344

345   VDD is wide-spread in the population, it has a negative impact on HRQoL with a burden of

346   disease that is much larger than rickets and osteomalacia. VDD and its complications are

347   preventable and well-planned public health strategies can be highly cost-effective and even

348   cost-saving. Biological, environmental, cultural, historical, and economic factors influence how

349   VDD affects the population, as well as the cost and effectiveness of alternative strategies.

350   Therefore, tackling population VDD in England and Wales requires efforts from

351   multidisciplinary professionals, such as clinicians, nutritionists, health economists, public

352   health professionals, and policy makers.

362   **Conflict of interest**

363   None declared

364   **Author Contributions**

365   All authors contributed to designing the research. MA conducted the research and analyzed

366   data supervised by LA, MP, WH and EF. All authors contributed substantially to writing the

367   paper, while MA and EF had primary responsibility for final content. All authors have read

368   and approved the final manuscript.

369

References

1.   Holick MF. The vitamin D epidemic and its health consequences. J Nutr. 2005/10/28. 2005;135(11):2739s-48s.

2.   Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, et al. National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014) . Public Health Engand and the Food Standards Agency ; 2016.

3.   Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab. 2016/01/09. 2016;101(2):394–415.

4.   Uday S, Fratzl-Zelman N, Roschger P, Klaushofer K, Chikermane A, Saraff V, et al. Cardiac, bone and growth plate manifestations in hypocalcemic infants: revealing the hidden body of the vitamin D deficiency iceberg. BMC Pediatr. 2018 Jun;18(1):183.

5.   Maiya S, Sullivan I, Allgrove J, Yates R, Malone M, Brain C, et al. Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. Heart. 2008;94(5):581–4.

6.   Patel J V, Chackathayil J, Hughes EA, Webster C, Lip GY, Gill PS. Vitamin D deficiency amongst minority ethnic groups in the UK: a cross sectional study. Int J Cardiol. 2012/11/13. 2013;167(5):2172–6.

7.   Uday S, Högler W. Prevention of rickets and osteomalacia in the UK: political action overdue. Arch Dis Child [Internet]. 2018; Available from: http://adc.bmj.com/content/archdischild/early/2018/04/16/archdischild-2018-314826.full.pdf

8.   Brown LL, Cohen B, Tabor D, Zappalà G, Maruvada P, Coates PM. The vitamin D paradox in Black Americans: a systems-based approach to investigating clinical practice, research, and public health - expert panel meeting report. BMC Proc [Internet]. 2018;12(6):6. Available from: https://doi.org/10.1186/s12919-018-0102-4

9.   Vatanparast H, Nisbet C, Gushulak B. Vitamin D insufficiency and bone mineral status in a

population of newcomer children in Canada. Nutrients [Internet]. 2013 May 14;5(5):1561–72. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23673607

10.	Bärebring L, Schoenmakers I, Glantz A, Hulthén L, Jagner Å, Ellis J, et al. Vitamin D status during pregnancy in a multi-ethnic population-representative Swedish cohort. Nutrients. 2016;8(10):655.

11.	Ramnemark A, Norberg M, Pettersson-Kymmer U, Eliasson M. Adequate vitamin D levels in a Swedish population living above latitude 63 N: The 2009 Northern Sweden MONICA study. Int J Circumpolar Health. 2015;74(1):27963.

12.	Andersson Å, Björk A, Kristiansson P, Johansson G. Vitamin D intake and status in immigrant and native Swedish women: a study at a primary health care centre located at 60 N in Sweden. Food Nutr Res. 2013;57(1):20089.

13.	Glerup H, Rytter L, Mortensen L, Nathan E. Vitamin D deficiency among immigrant children in Denmark. Eur J Pediatr. 2004;163(4):272–3.

14.	O'Callaghan KM, Kiely ME. Ethnic disparities in the dietary requirement for vitamin D during pregnancy: considerations for nutrition policy and research. Proc Nutr Soc. 2018;77(2):164–73.

15.	Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull [Internet]. 2014;39(4):322–50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4288313/

16.	(SACN) SAC on N. Vitamin D and Health [Internet]. Public Health England; 2016. Available from: https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition

17.	Uday S, Kongjonaj A, Aguiar M, Tulchinsky T, Högler W. Variations in infant and childhood vitamin D supplementation programmes across Europe and factors influencing adherence. Endocr Connect [Internet]. 2017 Sep 18;6(8):667–75. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28924002

18.	Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, et al. National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012). Public Health Engand and Food Standards Agency; 2014.

19.   Basatemur E, Sutcliffe A. Incidence of Hypocalcemic Seizures Due to Vitamin D Deficiency in Children in the United Kingdom and Ireland. J Clin Endocrinol Metab. 2014;100(1):E91–5.

20.   Julies P, Lynn RM, Pall K, Leoni M, Calder A, Mughal Z, et al. I16 Nutritional rickets presenting to secondary care in children (&lt;16 years) – a uk surveillance study. Arch Dis Child [Internet]. 2018 Mar 1;103(Suppl 1):A202 LP-A203. Available from: http://adc.bmj.com/content/103/Suppl_1/A202.3.abstract

21.   Cashman KD, Dowling KG, Skrabakova Z, Gonzalez-Gross M, Valtuena J, De Henauw S, et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr. 2016/02/13. 2016;103(4):1033–44.

22.   Darling AL, Hart KH, Macdonald HM, Horton K, Kang'Ombe AR, Berry JL, et al. Vitamin D deficiency in UK South Asian Women of childbearing age: a comparative longitudinal investigation with UK Caucasian women. Osteoporos Int. 2013;24(2):477–88.

23.   Martin CA, Gowda U, Renzaho AMN. The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis. Nutrition. 2016;32(1):21–32.

24.   van der Meer IM, Middelkoop BJC, Boeke AJP, Lips P. Prevalence of vitamin D deficiency among Turkish, Moroccan, Indian and sub-Sahara African populations in Europe and their countries of origin: an overview. Osteoporos Int [Internet]. 2011;22(4):1009–21. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3046351/

25.   Ginde AA, Liu MC, Camargo CA. Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988–2004. Arch Intern Med [Internet]. 2009 Mar 23;169(6):626–32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3447083/

26.   Aguiar M, Andronis L, Pallan M, Högler W, Frew E. Preventing vitamin D deficiency (VDD): a systematic review of economic evaluations. Eur J Public Health. 2017/02/17. 2017;27(2):292–301.

27.   Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. J Health Serv Res Policy. 2004;9(2):110–8.

28. Davis S, Stevenson M, Tappenden P, Wailoo AJ. NICE DSU Technical Support Document 15: Cost-effectiveness modelling using patient-level simulation. Sch Heal Relat Res Univ Sheff. 2014;

29. (NICE) NI for H and CE. Developing NICE guidelines: the manual [Internet]. 3rd ed. Process and methods [PMG20]. 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation

30. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task force-3. Value Heal. 2012;15(6):812–20.

31. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. Cost Eff Resour Alloc. 2013;11(1):6.

32. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.

33. Statistics O for N. Census. UK Data Serv Census Support. 2011;

34. Allen RE, Dangour AD, Tedstone AE, Chalabi Z. Does fortification of staple foods improve vitamin D intakes and status of groups at risk of deficiency? A United Kingdom modeling study. Am J Clin Nutr. 2015/07/03. 2015;102(2):338–44.

35. Research NS, Laboratory MRCEW, London UC, School M. National Diet and Nutrition Survey Years 1-6, 2008/09-2013/14 [Internet]. UK Data Services; 2017. Available from: http://doi.org/10.5255/UKDA-SN-6533-7

36. Allen RE. Would fortification of more foods with vitamin D improve vitamin D intakes and status of groups at risk of deficiency in the UK? London School of Hygiene & Tropical Medicine. London School of Hygiene & Tropical Medicine; 2013.

37. Limited T. FreeD: Vitamin D supplementation in Lewisham [Internet]. 2014. Available from: http://www.therapyaudit.com/media/2015/05/lewisham-casestudy.pdf

38.   Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev [Internet]. 2012;(9). Available from: http://dx.doi.org/10.1002/14651858.CD007146.pub3

39.   Aguiar M. Decision analytic modelling of the prevention of vitamin D deficiency in England and Wales [Internet]. UniversityoOf Birmingham; 2018. Available from: http://etheses.bham.ac.uk/8120/

40.   Food Standards Agency (FSA). Improving folate intakes of women of reproductive age and preventing neural tube defects: practical issues [Internet]. 2007. Available from: http://tna.europarchive.org/20120419000433/http://www.food.gov.uk/multimedia/pdfs/fsa0706 04.pdf

41.   NABIM. Statistics [Internet]. 2014. Available from: http://www.nabim.org.uk/statistics

42.   Roy S, Sherman A, Monari-Sparks MJ, Schweiker O, Hunter K. Correction of Low Vitamin D Improves Fatigue: Effect of Correction of Low Vitamin D in Fatigue Study (EViDiF Study). N Am J Med Sci [Internet]. 2014 Aug;6(8):396–402. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4158648/

43.   Santos AS, Guerra-Junior AA, Godman B, Morton A, Ruas CM. Cost-effectiveness thresholds: methods for setting and examples from around the world. Expert Rev Pharmacoecon Outcomes Res. 2018;18(3):277–88.

44.   Jentink J, van de Vrie-Hoekstra NW, de Jong-van den Berg LT, Postma MJ. Economic evaluation of folic acid food fortification in The Netherlands. Eur J Public Heal. 2008/02/02. 2008;18(3):270–4.

45.   Bentley TGK, Weinstein MC, Willett WC, Kuntz KM. A cost-effectiveness analysis of folic acid fortification policy in the United States. Public Health Nutr. 2009;12(04):455–67.

46.   Grosse SD, Berry RJ, Tilford JM, Kucik JE, Waitzman NJ. Retrospective Assessment of Cost Savings From Prevention. Am J Prev Med. 2016;50(5):S74–80.

47.   Basatemur E, Hunter R, Horsfall L, Sutcliffe A, Rait G. Costs of vitamin D testing and

prescribing among children in primary care. Eur J Pediatr [Internet]. 2017 Oct [cited 2018 May 24];176(10):1405–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28803270

48. Poole CD, Smith J, Davies JS. Cost-effectiveness and budget impact of Empirical vitamin D therapy on unintentional falls in older adults in the UK. BMJ Open. 2015;5(9):e007910.

49. Del Valle HB, Yaktine AL, Taylor CL, Ross AC. Dietary reference intakes for calcium and vitamin D. National Academies Press; 2011.

50. Zhang R, Li B, Gao X, Tian R, Pan Y, Jiang Y, et al. Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies. Am J Clin Nutr [Internet]. 2017 Apr [cited 2019 Apr 18];105(4):810–9. Available from: https://academic.oup.com/ajcn/article/105/4/810-819/4569717

51. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. [cited 2019 Apr 18]; Available from: http://dx.doi.org/10.1136/bmj.i6583

52. (IOM) I of M. Dietary reference intakes for calcium and vitamin D. National Academies Press; 2011.

53. Allen LH. Guidelines on food fortification with micronutrients. In: Guidelines on food fortification with micronutrients. World Health Organization. Dept. of Nutrition for Health and Development; 2006.

54. WHO FAO. Evaluating the public health significance of micronutrient malnutrition. Guidel food Fortif with Micronutr Geneva World Heal Organ. 2006;39–92.

55. Urrutia-Pereira M, Solé D. [Vitamin D deficiency in pregnancy and its impact on the fetus, the newborn and in childhood]. Rev Paul Pediatr [Internet]. 2015 [cited 2019 Apr 18];33(1):104–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25662013

56. Holick MF. The Influence of Vitamin D on Bone Health Across the Life Cycle. J Nutr [Internet]. 2005 Nov 1 [cited 2019 Apr 18];135(11):2726S-2727S. Available from: https://academic.oup.com/jn/article/135/11/2726S/4669897

57. Darnton-Hill I, Webb P, Harvey PWJ, Hunt JM, Dalmiya N, Chopra M, et al. Micronutrient deficiencies and gender: social and economic costs. Am J Clin Nutr [Internet]. 2005 May 1;81(5):1198S-1205S. Available from: http://dx.doi.org/10.1093/ajcn/81.5.1198

58. Bivins R. "The English Disease" or "Asian Rickets"?: Medical Responses to Postcolonial Immigration. Bull Hist Med. 2007;81(3):533.

59. Horton S. The Economics of Food Fortification. J Nutr [Internet]. 2006 Apr 1;136(4):1068–71. Available from: http://dx.doi.org/10.1093/jn/136.4.1068

60. Filby A, Wood H, Jenks M, Taylor M, Burley V, Barbier M, et al. Examining the Cost-Effectiveness of Moving the Healthy Start Vitamin Programme from a Targeted to a Universal Offering: Cost-effectiveness Systematic Review [Internet]. NICE, editor. Vol. July. 2015. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-guidelines/healthy-start-cost-effectiveness-review.pdf

Figures legends

Figure 1 – Illustration of the model structure

Figure 2 – Cost-effectiveness acceptability curve (CEAC) showing the probability of alternatives to prevent VDD being cost-effective at increasing acceptability thresholds