Clarion Journal of Infectious Diseases and Therapy [CJIDT]

Volume 2022 Issue 02

Short Commentary

The Persistent Disparity of Vitamin D Status between BAME and Other Britons could be Increasing COVID-19 Risks in those Communities

Barbara J Boucher, BSc, MD, FRCP

Hon Prof, The Blizard Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, UK

Received: June 23, 2022; **Accepted:** July 08, 2022; **Published:** July 22, 2022

Citation: Barbara J Boucher (2022) The Persistent Disparity of Vitamin D Status between BAME and Other Britons could be Increasing COVID-19 Risks in those Communities. *Clar J Infect Dis Ther* 03(02): 251–257.

Griffin et al. recently made a cogent case for increasing the SACN (Specialist Advisory Committee on Nutrition) recommended daily intakes of vitamin D_3 for the adult UK population, as used by other official UK advisory bodies, from the long- standing 400 IU/day to 800–1000 IU/day in order to reduce vitamin D deficiency rates and related health risks, possibly including Covid-19 severity. [1] Rickets and potentially fatal infantile hypocalcaemic fits and cardiomyopathy have been reported regularly in infants and young children amongst the south Asian diaspora arriving in the UK from the mid-20th Century. [2,3] Similarly, osteomalacia due to vitamin D deficiency(VDD) has been seen, especially in south Asian women covering their faces and arms as many amongst these British communities still do for cultural and religious reasons. [4]. Furthermore, the well-known increases in non-skeletal health problems in those groups, includingtype 2 diabetes, obesity, cardiovascular disease and early mortality, are all consistently reported as associating inversely with vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentrations). [5,6] Similarly, Covid-19 illness severity (hospital admission, need for intensive care and mortality) associates inversely with current and pre-existing vitamin D status (VitDS) generally and isrecognised to be more severe in dark-skinned Britons. [7,8] However, these well-known inverse associations are commonly taken to reflect 'reverse causation',[9] and to mean that there is no contributory role of vitamin D deficiency (VitDD) in the causality of such disorders despite the observational associations, an assumption thatthis commentary challenges.

VDD recognition in UK immigrant groups, initially south Asians, coincided with 25(OH)D assay development from the mid-20th century. [2,10] Mechanistic effects ofthe active hormonal metabolite, 1,25-dihydroxyvitamin D (Calcitriol) eventually provided an understanding of how vitamin D promotes bone health decades after the medical profession finally accepted that rickets was prevented and cured by both sunlight and cod-liver-oil, leading to the discovery of vitamins D_2 and D_3 in the 1920s. [2,11,12] Rickets was virtually abolished in the UK after the 'great depression' of the 1930s, from early in world war II (1941/2) by provision of cod-liver-oil amongst the 5 welfare foods for pregnant and nursing mothers and 1–5-year-old children (with extra milk, meat and eggs, each adding some vitamin D). Free cod-liver oil was then provided in antenatal clinics until its withdrawal in 1994 due to demonstrable teratogenicityof an excessive vitamin A content (since corrected), butwith no provision of alternative sources of vitamin D. This unfortunate situation allowed rickets to return, most commonly in dark-skinned Britons, (currently grouped as 'Black, south Asian and Mixed Ethic minorities' [BAME]), along with the frequently fatal problems of infantile hypocalcaemic fits and cardiomyopathy. [2,13]

It is well known that renal vitamin D activation forms hormonal calcitriol, essential for bone health through well understood mechanisms. However, this is as much as most people, including most health professionals, usually know about the effects of vitamin D. [14] Continuing research, however, has established that vitamin D is also necessaryfor

normal function in most tissues, and has elucidatedmany mechanisms involved that are induced through the identical activation of 25(OH)D to form calcitriol that is now known to take place within target tissues, thoughdifferently regulated. [15] Vitamin D signalling pathways modulating different intracellular effects of vitamin D are increasingly well understood, and 'triggered' through 3 basic mechanisms. 1) Rapid non-genomic effects following calcitriol-binding to cell membrane caveolar vitamin D receptors (VDRs) that raise intracellular ionised calcium (e.g., increasing islet beta cell insulin release). [16,17] 2) Slower genomic effects, mostly following the binding of ligand-bound-VDR:RXR complexes to nuclear VDR- response elements in the promoter regions of ~3000 human genes (e.g., increasing insulin secretion) [18,19] and 3), various types of epigenetic effect including many relevant to early life development and dependent on maternal vitamin D status, (e.g increasing pre-adipocyte differentiation, likely reducing adult obesity).[20] Other examples of known non-skeletal mechanistic effects of vitamin D include; reducing hepatic synthesis of triglycerides and hepatic glucose output and promotion of improved skeletal muscle function (together reducing insulin resistance); suppressing renin secretion (lowering blood pressure in the young and reducing tissue damagedue to excessive free radical production]; increasing innateimmune responses (by raising antimicrobial defensin[s] and cathelicidin secretion); preventing excessive acquiredimmune responses important in infections and in inflammatory disorder, including atheromatous arterial wall disease (by suppressing pro-inflammatory and stimulating anti-inflammatory-cytokine secretion and by suppressing the MMP2/9 secretion that aggravates plaque disruption); suppressing pro-carcinogenic processes (e.g increasing cell differentiation); promoting ACE2 receptor production in the lungs that is protective against ARDS (acute respiratory distress syndrome) a major risk in severe Covid-19 illness.[21–29]

Serum 25(OH)D concentrations (Vitamin D status [VitDS]) are reduced by obesity, partly through dilution into enlarged fat stores but also due to reduced activity/production of the specific hepatic 25-hydroxylase. Serum 25(OH)D levels are also reduced in diabetes due to increased production of the 24-hydroxylase enzyme catabolic for both 25(OH)D and calcitriol and of the FGF23 (fibroblast growth factor 23) that reduces intracellular calcitriol production by suppressing the activating 1α-hydroxylase. Severe illness also lowers serum 25(OH)D values by reducing hepatic 25-hydroxylase activity.[30,31]

Investigators carrying out vitamin D supplementation trials have generally assumed that their 'failure' confirmsthat the consistent associations of health outcomes withvitamin D status, often strongly supported by prospective data, are due to reverse causation. As a result, many investigators take it that the adverse effects of inadequateVitDS suggested by observational associations, and by mechanistic effects, must be without clinical significance. However, all target tissues relevant to health produce intracellular calcitriol in amounts relating directly to circulating 25(OH)D concentrations (the substrate for intracellular vitamin D activation).[1] 'Reverse confounding', therefore, will aggravate tissue disorders associated with low VitDS since reductions in VitDS (circulating 25(OH)D concentrations) must, necessarily, reduce autocrine and paracrine tissue effects dependent on locally produced calcitriol, whatever the mechanisms involved.

Failures of RCTs to confirm causality for many known mechanistic effects of vitamin D have often reflected unavoidable delays in the application of knowledge of vitamin D's biological effects to RCT design and analysis but the many 'negative trial results have led to the wide-spread view that such results confirm the irrelevanceof vitamin D status to human ill-health, as discussed above. However, such inferences can now be challenged for several reasons. Firstly, there are variations in serum 25(OH)D thresholds for different effects of vitamin D and, while it has long been assumed that health-effects will simply reflect supplemental dosages, in fact they depend on adequate correction of VDD for the condition of interest. [32,33] This is because association of effects with VDD is S-shaped rather than linear.[34] thus, no benefits are seen with supplementation in deficiency unless 25(OH)D values rise into the steep part of the S-shaped associations of effects/outcomes with VitDS and reach the threshold value needed for induction of the desired outcome (e.g., a serum 25(OH)D of 50 nmol/l for bone but 80–100 nmol/l for lowering insulinresistance).[35,36] Additionally, few health benefits can be expected with supplementation in vitamin D repletionwhere effects already lie along the upper plateaus of their S-shaped associational relationships. With

increasing appreciation of the implications of these facts, RCT re-analyses are increasingly reporting health benefits expected from adequate correction of VitDS. In the D2d study, for example, no T2DM risk reductions were found initially with supplementation at up to 4000 IU/day in pre-diabetes, but reanalysis by achieved VitDS revealed that those maintaining intra-trial serum 25(OH)D values of ≥100 nmol/l, (requiring daily intakes of 4000 IU/day) had up to 70% reductions in T2DM incidence.[37,38] Similarly, re-analysis of 25 earlier randomised controlled trials (RCTs) with variable results for upper respiratory tract infection (URTI) reductions, revealed significant risk reductions in those with baseline deficiency with daily supplementation but not with interval dosing.[39]

The information just discussed suggests that 25(OH) D reductions induced by disorders like obesity and diabetes create vicious circles aggravating health risks are likely to require higher vitamin D intakes for VDD correction. Support for this view is provided by the finding that correcting VDD requires higher vitamin D supplemental intakes in overweight and obese people than in the non-obese (by x1.5 and x2–3-fold respectively) and by the DD2d data reanalysis, showing that T2DM risk reduction would be impossible on current UK or US intake recommendations. Thus, for example, unless the UK acts to promote adequate vitamin D intakes and abolish deficiency, high T2DM prevalencerates will continue to be aggravated by deficiency.

Furthermore, since obesity increases T2DM risk, even higher intakes than 4000 IU/day may be needed for reduction in T2DM incidence rates in obese pre-diabetics. BAME Britons are known to need higher intakes than pale-skinned Britons as vitamin D synthesis is reduced by increased skin pigmentation and modest clothing and will be increased by their raised rates of both obesityand T2DM. Together these several problems must worsen VDD, aggravating associated health risks, likely including those for Covid-19 severity which are already known to be increased by obesity, T2DM and BAME ethnicity.[41–43]

VDD is a suggested risk factor for Covid-19 severity because it reduces protective immune responses to infection and reduces lung protection in ARDS, as mentioned above, Covid-19 illness is also associated with reduced D status at presentation. Covid-19 has, therefore, been treated with vitamin D, often with large bolus doses, with some possible benefits.[44–48] However, bolus-dosing rapidly upregulates effects protective against VitD toxicity, increasing 24-hydroxylase activity (catabolic for 25(OH)D and calcitriol) and increasing production of FGF-23, (known to inactivate the vitamin D activating 1a-hydroxylase) for at least 3 months. Thus, bolus-dose treatment failures are understandable as are their adverse effects +on bone and muscle health (increasing risks of falls and failing to prevent rickets).[49–51] Covid-19 survivors treated with bolus doses may, therefore, be atrisk of aggravation of 'long-COVID' by those adverseeffects. [52]

If vitamin D deficiency is a risk factor for Covid-19, then pre-infection repletion should be protective, as is suggested by reductions in infection rates in subjects with increasingly higher serum 25(OH)D values overthe year pre-infection in a large American cohort study and in UK biobank subjects 'habitually' taking vitaminD (but not other supplements) vs, no supplements]. [53,54] Reduced Covid-19 severity is reported with 25(OH)D (calcifediol) treatment of hospitalised patients and notably, slow-release oral 25(OH)D treatment does not increase catabolic 24-hydroxylase activity. A larger Spanish study of calcifediol usage also suggests beneficial effects with reductions in transfers to intensive care and in mortality rates.[55,56]

Unfortunately, the large and still evolving body of knowledge about the non-skeletal effects of vitamin D must be unfamiliar to many health professionals since UK VDD is being allowed to persist at such high rates (20–40%, as defined for bone health by a serum 25(OH) D <25 nmol/l); those high rates themselvesdemonstrating the lack of efficacy of the long-standing UK intake recommendations (at 400 IU/day), made without the provision of higher intakes for BAME and other high-risk groups (including the elderly, care home residents, shift workers and the obese).[57]

Current rates of deficiency are clearly undesirable, even if only as defined for bone health and UK mortality rates from Covid-19 have been amongst the highest reportedworld-wide.[58] Furthermore, the groups hardest hit byCovid-19 coincide with those recognised as at 'high-risk' for vitamin D deficiency, warranting urgent programmes to correct D deficiency generally, but most especially in groups currently in double-jeopardy for these risks.[59] Though increased

vitamin D deficiency rates in dark- skinned immigrant groups have been widely known and discussed they were often attributed to persisting cultural factors and non-assimilation of UK ways of life over the last 50 years,[2,60] explaining why no effective measureswere set up to increase their vitamin D intakes. Margarinewas fortified by statute when the south Asian diaspora reached the UK, but only to match butter content at 1.25 µg/100 grams.[13] This woeful situation has been described, historically, as reflecting that "*diet frequently became a proxy or shorthand for culture (and religion, and race), while disease justified pressure to assimilate*".[2] and remains uncorrected despite some local efforts and the 'Sure Start' scheme that hoped to reach all pregnantwomen from 2000, though supplements had to be claimed (often difficult for women not fluent in English), and often poorly taken up [13,61] while VDD rates in infants and children remain unacceptably high and admissions for hypocalcaemic emergencies have increased in recent years, mainly in babies of black and south Asian extraction.[62]

Many authors, and the Lawrence enquiry, have concluded that increased Covid-19 severity and mortality rates in BAME Britons reflects 'racial discrimination,' causing increased poverty, overcrowding, and other reductions in socio-economic status.[63,64] While itis undeniable that multiple socio-economic and health risk factors contribute to increased Covid-19 risks,vitamin D status was not considered in those reports. [63] When vitamin D status was included in a UK- Biobank data analysis large numbers of subjects untested for Covid-19 were used as negative controls for covid-19 positivity, adjustment was made for more factors than the data could support, and adjustments were made for factors specifically reducing 25(OH)D values (ethnicity, obesity and diabetes, see above) and, though baseline VitD deficiency 5 to 10 years pre-pandemic did predict increased Covid-19 risks, this variable was, unsurprisingly, eliminated by adjustment for the last 3 factors.[65, 66, 67]

NICE advises treating adult vitamin D deficiency (a serum 25(OH)D <25nmol/l) as follows "***Choose the most appropriate treatment regimen.*** *For the treatment of vitamin D deficiency, the recommended treatment is based on fixed loading doses of vitamin D (up to a total of about300,000 international units [IU]) given either as weekly or daily split doses, followed by lifelong maintenance treatmentof about 800 IU a day*" NICE also states *that "Several treatment regimens are available, including 50,000 IU once a week for 6 weeks (300,000 IU in total), 20,000 IU twice a week for 7 weeks (280,000 IU in total), or 4000 IU daily for 10 weeks (280,000 IU in total)".*[68] Thus, current UK intake recommendations,at 400 IU/day all year round, cannot be expected to correct the 40% overall UK deficiency rates or the increased deficiency rates seen in south Asian and Black Britons,[69] and the provision of 4 months supply of vitamin D at 400 IU/day to vulnerable groups in the UKfrom early 2021 is unlikely to reduce current VDD ratessignificantly.

Advice on short-term self-supplementation through the current pandemic at 1000–2000 IU/day for younger and older adults respectively, but at 2000–4000 IU/day in the first 2 weeks in high-risk groups would, however, be within UK safe intake levels.[70] It could also prove a useful adjunct for Covid-19 risk reduction by raising 25(OH)D values towards the 50–75 nmol/l recently reported as being the most protective against respiratory tract infections.[71] However, a long-term programme is also needed to abolish UK vitamin D deficiency, ideally through food fortification, perhaps of flours plus high-risk group supplementation, as already suggested,[72] (together with efficacy audits) as already achieved in Finland.[73,74] Such a programme would correct a long- standing failure of public health advice and correct the long-standing racial disparities in vitamin D status that can be regarded as discriminatory, and, additionally would have the potential to reduce the severity of futureviral pandemics.

References

1. Griffin G, Hewison M, Hopkin J, Kenny RA, Quinton R, Rhodes J, Subramanian S, Thickett D (2021) Preventing vitamin D deficiency during the COVID-19 pandemic: UK definitions of vitamin D sufficiency and recommended supplement dose are set too low. *Clin Med (Lond)* 21: e48-e51. [View]
2. Bivins R (2007) "The English disease" or "Asian rickets"? Medical responses to postcolonial immigration. *Bull Hist Med* 81: 533–68. [View]
3. Högler W (2015) Complications of vitamin D deficiency from the foetus to the infant: One cause, one prevention, but who's responsibility? *Best Pract Res Clin Endocrinol Metab* 29: 385–98. [View]

4. Darling AL (2020) Vitamin D deficiency in western dwelling South Asian populations: an unrecognised epidemic. *Proc Nutr Soc* 79: 259–271.[View]
5. Boucher BJ (2012) Is vitamin D status relevant to metabolic syndrome? *Dermatoendocrinol* 4: 22–24. [View]
6. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H (2020) Vitamin D and cardiovascular health. *Clin Nutr* [View]
7. Katz J, Yue S, Xue W (2020) Increased risk for COVID-19 in patients with vitamin D deficiency. *Nutrition* 84: 111106. [View]
8. Perez-Guzman PN, Daunt A, Mukherjee S, Crook P, Forlano R, Kont MD, Løchen A, Vollmer M, Middleton P, Judge R, Harlow C, Soubieres A, Cooke G, White PJ, Hallett TB, Aylin P, Ferguson N, Hauck K, Thursz MR, Nayagam S [2020] Clinical characteristics and predictors of outcomes of hospitalized patients with COVID-19 in a multi-ethnic London NHS Trust: a retrospective cohort study. *Clin Infect Dis* ciaa1091. [View]
9. A Dictionary of Epidemiology Pub M Porta. 6th Ed, 2014; ISBN-13; 978199976720: Oxford University Press. Latest E on-line eISBN; 9780199390069
10. Carter GD, Berry J, Durazo-Arvizu R, Gunter E, Jones G, Jones J, Makin HLJ, Pattni P, Sempos CT, Twomey P, Williams EL, Wise SA (2018) Hydroxyvitamin D assays: An historical perspective from DEQAS. *J Steroid Biochem Mol Biol* 177: 30–35. [View]
11. Gibbs D (1994) Rickets and the crippled child: an historical perspective. *J R Soc Med* 87: 729–32. [View]
12. Hunt M (1995) "Extraordinarily interesting and happy years": Martha M. Eliot and pediatrics at Yale, 1921–1935. *Yale J Biol Med* 68: 159–70. [View]
13. Hyppönen E, Boucher BJ (2010) Avoidance of vitamin D deficiency in pregnancy in the United Kingdom: the case for a unified approach in National policy. *Br J Nutr* 104: 309–14.[View]
14. Holick MF (1996) Vitamin D and bone health. *J Nutr* 126: 1159S-64S. [View]
15. (a) Hii CS, Ferrante A (2016) The Non-Genomic Actions of Vitamin D. *Nutrients* 8: 135. [View]. (b) Davidson HW, Peshavaria M, Hutton JC (1987) Proteolytic conversion of proinsulin into insulin. Identification of a Ca2+-dependent acidic endopeptidase in isolated insulin-secretory granules. *Biochem J* 246: 279–86. [View]
16. Mizwicki MT, Norman AW. Vitamin D Sterol/Vitamin D receptor Conformational Dynamics and Nongenomic actions:; Chapter 16:269–292 in Vitamin D, 4th edition. Ed. Feldman D, Wesley-Pike JM, Bouillon R, Giovannucci E, Golzman D, Hewison M. 2017. Vol. 1. Biochemistry, Physiology and Diagnostics.
17. Norman AW, Frankel JB, Heldt AM, Grodsky GM (1980) Vitamin D deficiency inhibits pancreatic secretion of insulin. *Science* 209: 823–5. [View]
18. Godfrey KM, Costello PM, Lillycrop KA (2016) Development, Epigenetics and Metabolic Programming. *Nestle Nutr Inst Workshop Ser* 85: 71–80. [View]
19. Chun RF, Adams JS, Hewison M (2008) Back to the future: a new look at 'old' vitamin D. *J Endocrinol* 198: 261–9. [View]
20. Abboud M, Gordon-Thomson C, Hoy AJ, Balaban S, Rybchyn MS, Cole L, Su Y, Brennan-Speranza TC, Fraser DR, Mason RS (2014) Uptake of 25-hydroxyvitamin D by muscle and fat cells. *J Steroid Biochem Mol Biol* 140: 232–6. [View]
21. Cheng S, So WY, Zhang D, Cheng Q, Boucher BJ, Leung PS (2016) Calcitriol Reduces Hepatic Triglyceride Accumulation and Glucose Output Through Ca2+/CaMKKβ/AMPK Activation Under Insulin-Resistant Conditions in Type 2 Diabetes Mellitus. *Curr Mol Med* 16: 747–758. [View]
22. Pramono A, Jocken JWE, Blaak EE (2019) Vitamin D deficiency in the aetiology of obesity-related insulin resistance. *Diabetes Metab Res Rev* 35: e3146. [View]
23. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP (2002) 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 110: 229–38.[View]
24. Bishop E, Ismailova A, Dimeloe SK, Hewison M, White JH (2020) Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. *JBMR Plus* 5: e10405. [View]
25. Norman PE, Powell JT (2005) Vitamin D, shedding light on the development of disease in peripheral arteries. *Arterioscler Thromb Vasc Biol* 25: 39–46. [View]
26. Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, et al. (2002) Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *QJM* 95: 787–96. [View]
27. Charoenngam N, Holick MF (2020) Immunologic Effects of Vitamin D on Human Health and Disease. *Nutrients* 12: 2097. [View]
28. Girgis CM, Clifton-Bligh RJ, Turner N, Lau SL, Gunton JE (2014) Effects of vitamin D in skeletal muscle: falls, strength, athletic performance and insulin sensitivity. *Clin Endocrinol (Oxf)* 80: 169–81. [View]
29. Malek Mahdavi A (2020) A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: Implications for a potential treatment for COVID-19. *Rev Med Virol* 30: 2020 [View]

30. Bouillon R, Bikle D. (1992) Vitamin D Metabolism Revised: Fall of Dogmas. J Bone Miner Res. 34:1985-1992. doi: 10.1002/jbmr.3884. [View]
31. Mata-Granados JM, Vargas-Vasserot J, Ferreiro-Vera C, Luque de Castro MD, Pavón RG, Quesada Gómez JM (2010) Evaluation of vitamin D endocrine system (VDES) status and response to treatment of patients in intensive care units (ICUs) using an on-line SPE-LC-MS/MS method. *J Steroid Biochem Mol Biol* 121: 452–5. [View]
32. Scragg R (2018) Emerging Evidence of Thresholds for Beneficial Effects from Vitamin D Supplementation. *Nutrients* 10: 561. [View]
33. Grant WB, Boucher BJ. (2019). Why Secondary Analyses in Vitamin D Clinical Trials Are Important and How to Improve Vitamin D Clinical Trial Outcome Analyses-A Comment on "Extra-Skeletal Effects of Vitamin D, Nutrients 11, 1460". *Nutrients*. 11:2182. [View]
34. Heaney RP (2012) The nutrient problem. Nutr Rev 70: 165–9.[View]
35. https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition. 2016.
36. Hurst PR, Stonehouse W, Coad J (2010) Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. *Br J Nutr* 103: 549–55. [View]
37. Pittas AG, Dawson-Hughes B, Sheehan P, Ware JH, Knowler WC, Aroda VR, et al. (2019) Vitamin D Supplementation and Prevention of Type 2 Diabetes. *N Engl J Med* 381: 520–530.
38. Dawson-Hughes B, Staten MA, Knowler WC, Nelson J, Vickery EM, et al. (2020) Intratrial Exposure to Vitamin D and New-Onset Diabetes Among Adults With Prediabetes: A Secondary Analysis From the Vitamin D and Type 2 Diabetes (D2d) Study. *Diabetes Care* 43: 2916–2922.
39. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 356: i6583.
40. Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ (2014) The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. *PLoS One* 9: e111265. [View]
41. Sutherland JP, Zhou A, Leach MJ, Hyppönen E (2020) Differences and determinants of vitamin D deficiency among UK biobank participants: A cross-ethnic and socioeconomic study. *Clin Nutr* [View]
42. Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, et al. (2013) The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited) -- a prospective population-based study. *J Am Coll Cardiol* 61: 1777–86. [View]
43. https://www.cbsnews.com/news/covid-19-new-diabetes-cases-linked *[02/02/2021]*
44. Katz J, Yue S, Xue W (2020) Increased risk for COVID-19 in patients with vitamin D deficiency. *Nutrition* 84: 111106. [View]
45. Brenner H (2021) Vitamin D Supplementation to Prevent COVID-19 Infections and Deaths-Accumulating Evidence from Epidemiological and Intervention Studies Calls for Immediate Action. *Nutrients* 13: 411. [View]
46. Tarazona-Santabalbina FJ, Cuadra L, Cancio JM, Carbonell FR, Garrote JMP, et al. (2021) VitaminD supplementation for the prevention and treatment of COVID-19: a position statement from the Spanish Society of Geriatrics and Gerontology. *Rev Esp Geriatr Gerontol* [View]
47. Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S (2020) Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. *Sci Rep* 10: 20191. [View]
48. https://clinicalmolecularallergy.biomedcentral.com/articles/10.1186/s.....
49. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, et al. (2020) Effect of calcidiol treatment and best available therapy on intensive care admission and mortality among patients hospitalized for COVID-19: A pilot randomised clinical study. *J Ster Biochem Mol Biol* [View]
50. Griffin G, Hewison M, Hopkin J, Kenny RA, Quinton R, Rhodes J, et al. (2021) Perspective: Vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: implications for COVID-19. *Clin Med (Lond)* [View]
51. Feng F, Shi G, Chen H, Jia P, Bao L, Xu F, Sun QC, Tang H. (2021) Comprehensive Interventions Including Vitamin D Effectively Reduce the Risk of Falls in Elderly Osteoporotic Patients. *Orthop Surg*;13:1262–1268
52. Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG (2021) Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It? *Lung* 11: 1–7. [View]

53. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF (2020) SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One* 15: e0239252. [View]

54. Ma H, Zhou T, Heianza Y, Qi L (2021) Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank. *Am J Clin Nutr* nqaa381. [View]

55. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, et al. (2020) "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *J Steroid Biochem Mol Biol* 203: 105751. [View]

56. Nogues X, Ovejero D, Pineda-Moncusí M, Bouillon R, Arenas D, Pascual J, et al. (2021) Calcifediol treatment and COVID-19-related outcomes. *J Clin Endocrinol Metab* dgab405. [View]

57. https://www.gov.uk/government/publications/sacn-rapid-reView-vitamin-d...December *2020*

58. https://www.bing.com/search?q=Coronavirus%2C+website%2C+ worldometer&

59. Alshahawey M (2020) COVID-19 and Vitamin D deficiency; the two pandemics. Are they correlated? *Int J Vitam Nutr Res* 1–2. [View]

60. Bivins R (2014) Ideology and disease identity: the politics of rickests, 1929–1982. *Med Humanit* 40: 3–10. [View]

61. Avis M, Bulman D, Leighton P (2007) Factors affecting participation in Sure Start programmes: a qualitative investigation of parents' views. *Health Soc Care Community* 15: 203–11. [View]

62. Basatemur E, Sutcliffe A (2015) Incidence of hypocalcemic seizures due to vitamin D deficiency in children in the United Kingdom and Ireland. *J Clin Endocrinol Metab* 100: E91–5. [View]

63. https://arc-w.nihr.ac.uk/Wordpress/wp-content/uploads/2020/05/COVID-19-Partner-report-BAME-communities-BCC001.pdf

64. The Lawrence review. 2020. https://labour.org.uk/review-into-the-impact-of-covid19-on-bame-communities

65. Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, et al. (2020) Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr* 14: 561–565. [View]

66. Boucher BJ (2020) Vitamin D status as a predictor of Covid-19 risk in Black, Asian and other ethnic minority groups in the UK. *Diabetes Metab Res Rev* 36: e3375. [View]

67. Pell JP, Hastie CE, Sattar N. Reply to letter to the editor, Davies et al. (2021) re "Vitamin D concentrations and COVID-19 infection in UK Biobank" (Hastie et al.). *Diabetes Metab Syndr* [View]

68. NICE (2020) https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults-treatment-prevention

69. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, et al. (2019) Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol* 180: P23-P54. [View]

70. Griffin G, Hewison M, Hopkin J, Kenny R, Quinton R, Rhodes J, Subramanian S, Thickett D (2020) Vitamin D and COVID-19: evidence and recommendations for supplementation. *R Soc Open Sci* 7: 201912. [View]

71. Jolliffe DA, Camargo CA, Sluyter JD, Aglipa M, Aloia JF, Ganmaa D, Bergman P, et al. (2020) Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials. *medRxiv* [View]

72. Aguiar M, Andronis L, Pallan M, Högler W, Frew E (2020) The economic case for prevention of population vitamin D deficiency: a modelling study using data from England and Wales. *Eur J Clin Nutr* 74: 825–833. [View]

73. Pietinen P, Männistö S, Valsta LM, Sarlio-Lähteenkorva S (2010) Nutrition policy in Finland. *Public Health Nutr* 13: 901–6. [View]

74. Itkonen ST, Andersen R, Björk AK, Brugård Konde Å, et al. (2020) Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries. *Scand J Public Health* 9: 1403494819896878. [View]

***Corresponding author:** Barbara J Boucher, The Blizard Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, UK;

Email: bboucher@doctors.org.uk