

# Vitamin D and COVID-19 in older age:

evidence versus expectations

The current global pandemic of SARS-CoV-2 coronavirus infection originated in Wuhan, China, during December 2019; over 50 million cases have been diagnosed to date. Older age and comorbidity have proven to be key markers of risk for severity of COVID-19 and mortality,<sup>1,2</sup> and residents of care homes have been proven to be at high risk. The Office for National Statistics has recorded 16 111 deaths related to COVID-19 in care home residents in England up to 20 November 2020.<sup>3</sup> In the first wave of the pandemic, 46% of all excess deaths in England and Wales up to 7 August occurred in care homes.<sup>4</sup> Older age is associated with increasing prevalence of vitamin D deficiency, which can affect up to 40% of care home residents.<sup>5</sup> There is considerable overlap between the non-modifiable risk factors for severe SARS-CoV-2 infection and those associated with deficiency of vitamin D. For example, age, ethnicity, diabetes, and chronic pulmonary and cardiac diseases; in addition, there is the observed trend towards greater severity of disease in northern latitudes. While these could imply an association between reduced vitamin D levels and susceptibility to SARS-CoV-2 infection this may simply be an ecological fallacy.<sup>6</sup> Therefore, it is important to understand the strength of evidence provided by epidemiological and observational studies of COVID-19, and compare it with what is known from clinical trials of the impact of vitamin D supplementation on acute respiratory infections, including those due to SARS-CoV-2.

### EXPECTATIONS AND MEDIA

Media articles extolling the benefits of vitamin D supplementation in preventing COVID-19 are plentiful. Existing guidelines promote vitamin D supplementation in older adults at risk, including those living in care homes, who experience limited light exposure.<sup>7</sup> Advice from Public Health England reiterating this during lockdown, due to restricted time outdoors, has become

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conflated with impressions that vitamin D has a direct impact on the course of COVID-19. Recent confused statements by the Secretary of State for Health and Social Care regarding the status of trials of vitamin D for prevention of COVID-19 have not helped; however, up-to-date rapid evidence reviews have concluded that there is no robust evidence base in older adults to recommend vitamin D supplementation for the prevention or treatment of COVID-19.<sup>8</sup>

### EVIDENCE — EPIDEMIOLOGY AND INTERVENTIONS

Reduced vitamin D levels are associated with increased risks of respiratory tract infections.<sup>9</sup> Geographical, ethnic, and age variations in COVID-19 infections and severity have prompted further research into the potential role of vitamin D; a negative correlation has been observed between estimated national mean vitamin D levels and SARS-CoV-2 infections and deaths in 20 European countries.<sup>10</sup> Further observational studies, taking account of ethnicity, have linked viral respiratory infection and severity of COVID-19 with deficiency of vitamin D.<sup>11,12</sup> A newly updated systematic review continues to show a modest protective effect for vitamin D supplementation on acute respiratory tract infections; however, caution in extrapolating this effect to SARS-CoV-2 infection is emphasised.<sup>13</sup> Organisational factors in care homes, such as sharing of agency staff and numbers of professional or lay visitors, have posed additional infection risks during the pandemic, independent of vitamin D status.

Plausible pathophysiological mechanisms

have been identified that might account for any association between deficiency of vitamin D and increased risks from SARS-CoV-2, and some evidence exists for beneficial effects with other coronavirus infections.<sup>8</sup> Vitamin D deficiency has been linked to immune-dysregulation;<sup>1</sup> it plays a role in regulating both innate and adaptive immunity, and immune cell proliferation.<sup>14</sup> Although recently updated meta-analytic evidence continues to suggest a modest protective effect against acute respiratory infections for a daily vitamin D dose equivalent of 400–1000 international units (IU) (odds ratio 0.70; 95% confidence interval = 0.55 to 0.89),<sup>13</sup> there are to the authors' knowledge, to date, no published adequately powered trial results examining the impact of vitamin D supplementation on COVID-19-related morbidity and mortality as a primary outcome. Early quasi-experimental pilot evidence suggests a short-term protective effect of prior vitamin D bolus dosing in French older adults living in care homes, resulting in reduced mortality over a mean 36 days of follow-up.<sup>15</sup> Many further studies are in progress,<sup>6</sup> and large trials addressing a testing and treating strategy, such as the CORONAVIT study, are directly relevant to primary care and may provide clarity on this intervention in the future.<sup>16</sup>

### WORKLOAD

Should trials support the mass testing of older people for vitamin D deficiency as an intervention to prevent acute respiratory tract infections (whether due to SARS-CoV-2 or other infectious causes), this would create significant additional workload and costs for primary care, care homes, and laboratories. Any requirement to determine vitamin D status prior to offering supplementation would present a significant barrier to the roll out of a future intervention. Current National Institute for Health and Care Excellence guidance promotes vitamin D supplementation to specific groups without testing for deficiency, unless symptoms or a very high risk of

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deficiency are identified; however, these recommendations are characterised by poor adherence. These groups include (but are not restricted to) pregnant and breastfeeding women, people aged over 65, people with low exposure to the sun by virtue of being housebound, or who cover their skin for cultural reasons. Supplementation for people of African, African-Caribbean, or South Asian family origin is also emphasised.<sup>7</sup> These are groups of people who are also at risk of more severe outcomes from COVID-19.<sup>1,2</sup>

## RECOMMENDATIONS

Prevalence of vitamin D deficiency, especially during the winter, is known to be high, and vitamin D supplements are widely available both over the counter and at low acquisition costs to the NHS, typically costing less than £3 (£3.4, \$4) per month.<sup>17</sup> Therefore, a pragmatic approach during the current pandemic and arguably in perpetuity, is to ensure that we effectively promote preventative supplementation of vitamin D at 400 IU/day across the UK. This is justified on the basis of known effects on bone health and consistent with existing guidance.<sup>7</sup>

There is a low risk of harm attached to this strategy, and any side-benefit of reducing the impact of COVID-19 in vulnerable groups may also be achieved.

On 28 November 2020, the Department of Health and Social Care announced plans to supply free vitamin D supplements to 2.7 million clinically extremely vulnerable people and care home residents for this winter.<sup>18</sup> While we should be mindful that the current evidence base for specific COVID-19 benefits from vitamin D supplementation is weak, we can support our patients in opting in to this service and also encourage people excluded from the clinically extremely vulnerable list to obtain and to start taking supplements.

Vitamin D supplementation represents one potentially useful intervention among many in the campaign against COVID-19. Research, including adequately powered trials, is already under way and the results must be awaited.

Given the known immunochemistry of vitamin D, potential anti-viral effects may be anticipated and support its potential utility as a cheap, available, and accessible therapeutic intervention for vulnerable members of the population.

### Christopher E Clark,

Clinical Senior Lecturer in General Practice, Primary Care Research Group, Institute of Health Services Research, University of Exeter Medical School, Exeter.

### Jane Masoli,

Clinical Doctoral Fellow and Specialist Registrar in Geriatric Medicine, Primary Care Research Group, Institute of Health Services Research, University of Exeter Medical School, Exeter.

### Fiona C Warren,

Senior Lecturer in Medical Statistics, Primary Care Research Group, Institute of Health Services Research, University of Exeter Medical School, Exeter.

### James Soothill,

Consultant Microbiologist, Camelia Botnar Laboratories, Great Ormond Street Hospital for Children NHS Trust, London.

### John L Campbell,

Professor of General Practice and Primary Care, Primary Care Research Group, Institute of Health

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## ADDRESS FOR CORRESPONDENCE

### Christopher E Clark

Primary Care Research Group, University of Exeter Medical School, Smeall Building, St Luke's Campus, Magdalen Rd, Exeter EX1 2LU, UK.

Email: [c.e.clark@exeter.ac.uk](mailto:c.e.clark@exeter.ac.uk)

Services Research, University of Exeter Medical School, Exeter.

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