Nutritional status, immunity & gut health in COVID-19

May 2021

Justine Bold

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

University of Worcester
www.worcester.ac.uk

Affiliations, declarations of interest

University of Worcester –Senior Lecturer on MSc on Nutritional Therapy MSc since Jan 2008.

Cardiff University in the Medical School, Centre For Medical Education - Programme Director of CPD.

Practiced as NT since 2003 (MBANT/CNHC) - Graduated in NT from BCNH

Assessor for NTEC

Working towards PhD by portfolio

@justineboldfood

justine_bold

Nutrition Health Worcester

This session

- Nutritional status and immunity
- Effects of pandemic on nutritional status
- Nutritional status in respiratory infection and COVID-19
- Assessing nutritional status
- Obesity
- Microbiome
- Nutritional factors associated with prolonged illness or hospitalisation and treatment in intensive care
- Recovery - long covid ongoing nutritional needs and support

Approach

- To present the journal article so reference is provided and can be looked up. References on the slides or follow.
- Not there to read every word in presentation
- Discuss main points of evidence.
  Look at latest evidence.

Insights from practice through to research and publication to help understand topics more and look at wider evidence base

Values…

Don't want to imply that anyone who has been ill or died as a result of COVID-19 had bad or unhealthy habits.

The virus can affect anyone and so much about what dictates body's response is still unknown.

Sensitive topic and many people have experienced loss or significant illness.

Long term research interest in malabsorption and links to many health conditions…

Working at medical school at Cardiff led me to work on wounds and infection

Review on wound care published 2020

Highlights links between malnutrition and infection

Supporting evidence-based practice in nutrition and hydration

KEY WORDS
- Dietitians
- Evidence
- Guidance
- Hydration
- Nutrition

The aim of this review is to synthesise literature on food, nutritional status and wound healing to help inform those working in wound care. A literature search was performed on PubMed, Scopus and EMBASE databases. Studies were critically appraised and the findings were analysed by narrative synthesis. Nutritional assessment is important in practice as nutritional status can impact on wound healing in several ways (including affecting both healing time and susceptibility to infection). There is widespread recognition of the importance of nutritional assessment tools, however, completion can sometimes be overlooked in practice. Healthcare professionals also need to be aware that obesity may be accompanied by micronutrient deficiency causing low micronutrient levels, however, nutritional assessment tools using body mass index (BMI) and weight loss may not identify this. Although there are intervention studies using nutritional formulations, such as amino acids, to support wound healing, the results of this review suggest that future research around using food as therapy and specific nutritional supplementation is needed.

JUSTINE BOLD
Programme Director of Continuing Professional Development in the Centre For Medical Education, Medical School, Cardiff University
Senior Lecturer School of Allied Health & Community University of Worcester

Wound care currently represents a significant issue in healthcare in the UK. Over a decade ago, in 2008, Posnett and Franks estimated that the cost of caring for patients with chronic wounds in the UK from 2005–2006 was between £2.3–£3.1 billion a year. A few years later, it was reported that dressings alone accounted for at least £120million in primary care costs (National Prescribing Centre, 2010). Scallon et al also reported in 2013 that £400m was spent on venous leg ulcers in the UK. Moreover, wounds impact on the lives of hundreds of thousands of people. In 2004, Bennett et al (2004) estimated that 412,000 people in the UK develop a new pressure ulcer annually and estimate 150,000 people within the UK have active venous ulcers. Wound care is also an important issue due to ageing populations; this in itself places extra demands on healthcare resources whilst lessening the availability of revenue available to support healthcare through taxation (Phillips, 2005). This highlights the need for cost-effective strategies that both prevent complications and support recovery, reducing healing times where-ever possible.

AIMS

The aims of this review are to consider the relationship between wound healing and nutritional status in both acute and chronic wounds, including pressure ulcers and diabetic foot ulcers, in the hope of informing healthcare practice and increasing the awareness of the importance of consideration of nutrition in a multidisciplinary approach. With economic austerity in the UK through much of the last decade, ongoing healthcare funding issues and the increasing emphasis at a policy level on patient centred-care, prevention and minimisation of complications would undoubtedly be considered best practice. The author aims to demonstrate how assessment of nutritional status of patients combined with an awareness of the prevalence of nutritional deficiencies and how they may impact on wound healing are worthy considerations to inform clinical approaches.

APPROACH

A narrative approach has been used to synthesise findings from a literature search using search

Narrative review on Covid developed with colleagues Miranda Harris, Lindsey Fellows and Manal Couchane at Worcester published 2020

Wrote this in Lockdown 1 – submitted June 2020

Gastroenterology and Hepatology From Bed to Bench.

REVIEW ARTICLE

Nutrition, the digestive system and immunity in COVID-19 infection

Justine Bold[1,2], Miranda Harris[*1], Lindsey Fellows[1], Manal Chouchane[1]
[1]*School of Allied Health & Community, University of Worcester, Worcester, WR2 6AJ, UK*
[2]*Centre for Medical Education, Medical School, Cardiff University, Cardiff, CF14 4YS, UK*
[*]**Equal to first author**

ABSTRACT

The current review aimed to synthesize the literature on the complex relationship between food consumption and nutritional status as well as the digestive system in order to examine the relationship between immunity and potential responses to COVID-19 infection. The goal is to help inform the many healthcare professionals working with COVID-19 patients. A literature search was performed on PubMed, Scopus, and EMBASE databases. Hand searches were also undertaken using Google and reference lists to identify recent evidence. Studies were critically appraised, and the findings were analyzed by narrative synthesis. Nutritional status can impact immunity in several ways, including affecting susceptibility to infection, severity of disease, and recovery time, and is therefore a significant consideration in the management of COVID-19. COVID-19 can also impact digestive function, which can further impact nutritional status. The role of Vitamin D deficiency in vulnerability to severe respiratory infections, including COVID-19, has been recognized, and it may have a role in treatment where deficiency is indicated. Healthcare professionals should be aware that obesity may be accompanied by micronutrient malnutrition including vitamin D deficiency and alterations in the microbiome and inflammatory responses, which can further impact immunity and disease severity. Multidisciplinary team-work is recommended in the management of patients with COVID-19, and approaches should include a consideration of nutritional status (both macronutrients and micronutrients), body weight, and gastrointestinal signs and symptom.

Keywords: Obesity, COVID-19, Nutritional status, Vitamin D, Microbiome, Multidisciplinary, Supplementation, Practice.
(Please cite as: **Bold J, Harris M, Fellows L, Chouchane M. Nutrition, the digestive system and immunity in COVID-19 infection. Gastroenterol Hepatol Bed Bench 2020;13(4):331-340).**

Introduction

[1] The COVID-19 pandemic is a novel infection and a major global healthcare challenge which highlights the need for cost-effective strategies that both prevent complications and support recovery, reducing recovery times and complications wherever possible. The current review aims to consider the relationship between COVID-19 infection and nutritional status, including obesity, and the broader impact it may have on both digestive function and gastrointestinal (GI) symptoms of COVID-19 infection. It is hoped this will inform all areas of healthcare practice and increase awareness of the importance of considering nutrition in a multidisciplinary approach.

Received: 21 June 2020 *Accepted*: 18 July 2020
Reprint or Correspondence: **Justine Bold,** PhD**.** *School of Allied Health & Community, University of Worcester, Worcester, WR2 6AJ, UK.*
E-mail: j.bold@worc.ac.uk
ORCID ID: 0000-0003-2439-8108

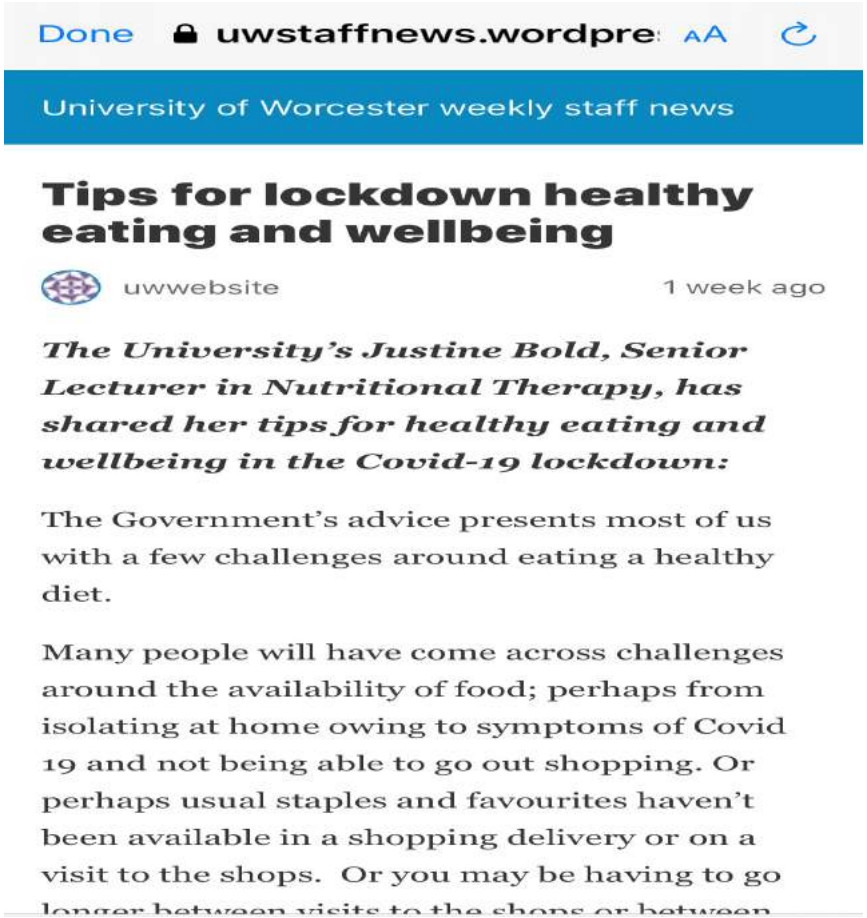
Method and Approach

A narrative approach has been used to synthesize findings from a literature search using search terms such as COVID-19 and nutritional status, obesity, malnutrition, nutritional deficiency, vitamin D, and microbiome. PubMed, Scopus and EMBASE databases were used and hand searches were also undertaken using Google and reference lists to identify recent evidence. Studies were critically appraised, and the findings were analyzed by narrative synthesis.

Malnutrition

The nutritional status of populations is recognized as a key factor influencing resilience against destabilization in the current COVID-19 pandemic (1). Community resilience is generally considered to be the ability to recover from adverse events (2). Malnutrition is an established risk factor for lowered immunity (3), and a hospital stay can increase a patient's chances of both

Wrote nutrition tips on COVID-19 in UK lockdown 1



Done uwstaffnews.wordpre AA

University of Worcester weekly staff news

Tips for lockdown healthy eating and wellbeing

uwwebsite 1 week ago

The University's Justine Bold, Senior Lecturer in Nutritional Therapy, has shared her tips for healthy eating and wellbeing in the Covid-19 lockdown:

The Government's advice presents most of us with a few challenges around eating a healthy diet.

Many people will have come across challenges around the availability of food; perhaps from isolating at home owing to symptoms of Covid 19 and not being able to go out shopping. Or perhaps usual staples and favourites haven't been available in a shopping delivery or on a visit to the shops. Or you may be having to go longer between visits to the shops or between

https://uwstaffnews.wordpress.com/2020/05/26/tips-for-lockdown-healthy-eating-and-wellbeing/

Delivered free webinars for Cardiff – designed for nurses/medics working frontline– on healthy eating for resilience

https://www.youtube.com/watch?v=X2wDLabHq4M&t=242s

Our review started with malnutrition

Introduction

[1] The COVID-19 pandemic is a novel infection and a major global healthcare challenge which highlights the need for cost-effective strategies that both prevent complications and support recovery, reducing recovery times and complications wherever possible. The current review aims to consider the relationship between COVID-19 infection and nutritional status, including obesity, and the broader impact it may have on both digestive function and gastrointestinal (GI) symptoms of COVID-19 infection. It is hoped this will inform all areas of healthcare practice and increase awareness of the importance of considering nutrition in a multidisciplinary approach.

Received: 21 June 2020 *Accepted*: 18 July 2020
Reprint or Correspondence: **Justine Bold,** [redacted] *School of Allied Health & Community, University of Worcester, Worcester, WR2 6AJ, UK.*
E-mail: j.bold@worc.ac.uk
ORCID ID: 0000-0003-2439-8108

Method and Approach

A narrative approach has been used to synthesize findings from a literature search using search terms such as COVID-19 and nutritional status, obesity, malnutrition, nutritional deficiency, vitamin D, and microbiome. PubMed, Scopus and EMBASE databases were used and hand searches were also undertaken using Google and reference lists to identify recent evidence. Studies were critically appraised, and the findings were analyzed by narrative synthesis.

Malnutrition

The nutritional status of populations is recognized as a key factor influencing resilience against destabilization in the current COVID-19 pandemic (1). Community resilience is generally considered to be the ability to recover from adverse events (2). Malnutrition is an established risk factor for lowered immunity (3), and a hospital stay can increase a patient's chances of both

Bold J, Harris M, Fellows L, Couchane M, Nutrition the digestive system and immunity in COVID-19 infection. Gastroenterology hepatology bed to bench. Abstract published – full article in production. https://journals.sbmu.ac.ir/ghfbb/index.php/ghfbb/article/view/2094

Malnutrition in UK

- Pre-pandemic @ 3million people in the UK at risk of malnutrition (Allied Health Professionals (AHP) 2012 and British Dietetic Association (no date).

- The BDA estimate 93% of these are living in their own home, whilst 5% are living in care homes and only 2% of these are in hospital.

- Established risk factor for infection and reduced immunity (BDA, 2019) and in hospital stays it increases the chance of complications and re-admission (Frank et al., 2015).

References follow…

References

Allied Health QIPP and ONS toolkit – a guide for healthcare commissioners.' Endorsed by all AHP colleges including the BDA and the RCSLT. Professionals 2012 https://www.networks.nhs.uk/nhs-networks/ahp-networks/ahp-qipp-toolkits

British Dietetic Association Malnutrition Food Fact sheet. 2019. Available at https://www.bda.uk.com/uploads/assets/a3b7670b-7f77-4a9f-b5bf14179882b6d1/Malnutrition-food-fact-sheet.pdf [Date accessed 14th February 2020].

Frank M, Sivagnanaratnam A, Bernstein J Nutritional assessment in elderly care: a MUST! *BMJ Qual Improv Rep* 2015 4(1): pii: u204810.w2031

Malnutrition in UK

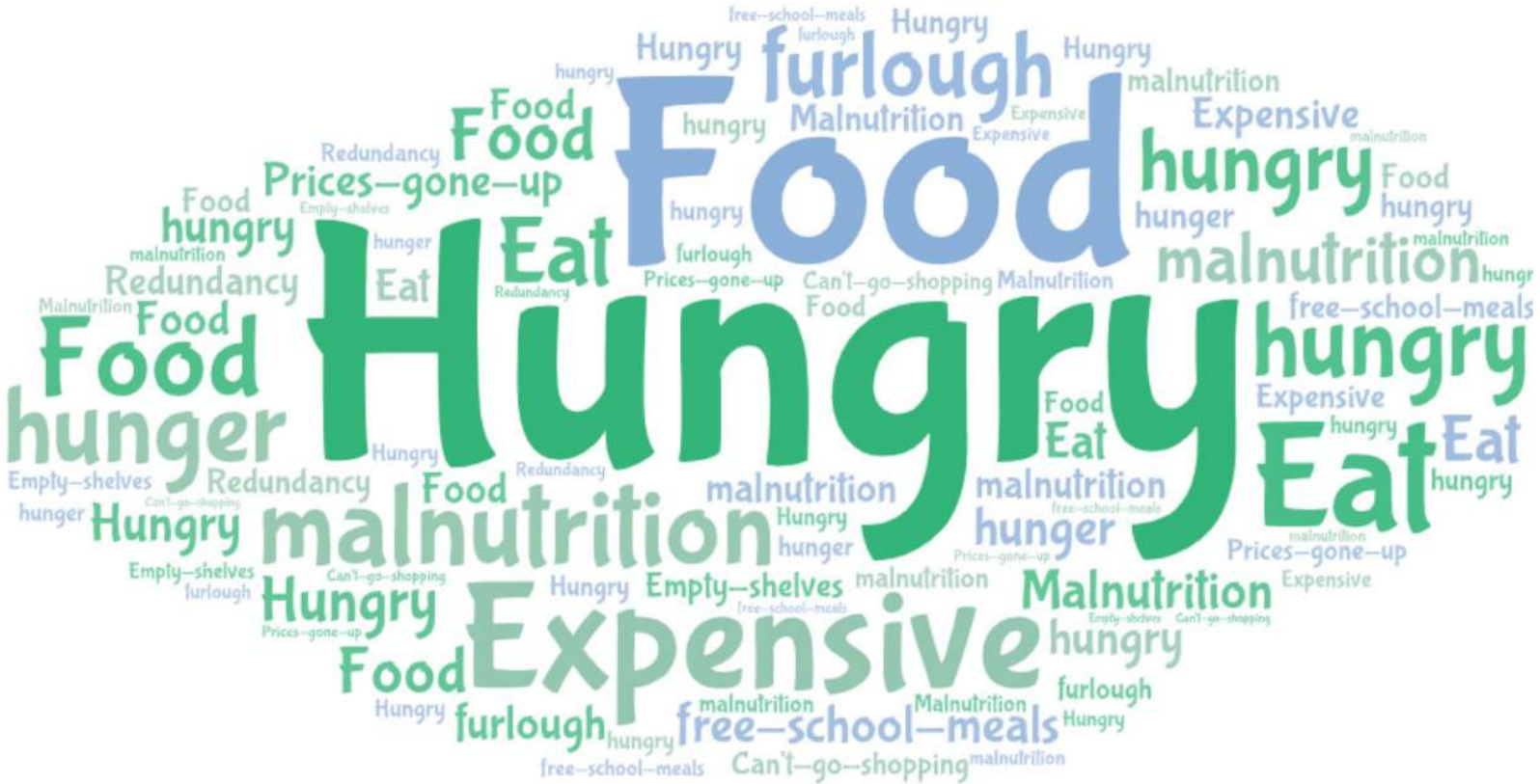
- Obesity as a state of malnourishment?

  World Health Organization refer to this as the ‘double burden of malnutrition’.

  People may be malnourished through food and calorie deficit whilst others maybe overfed but deplete in micronutrients.

- https://www.who.int/nutrition/double-burden malnutrition/en/#:~:text=The%20double%20burden%20of%20malnutrition,populations%2C%20and%20across%20the%20lifecours
-

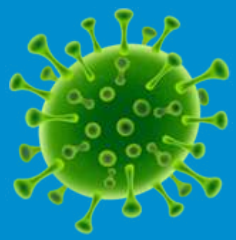
Effects of pandemic on malnutrition and nutritional status?



UK

3 main periods of national lockdown with closure of non-essential businesses and schools

- Furlough scheme
- Business closures
- Redundancies



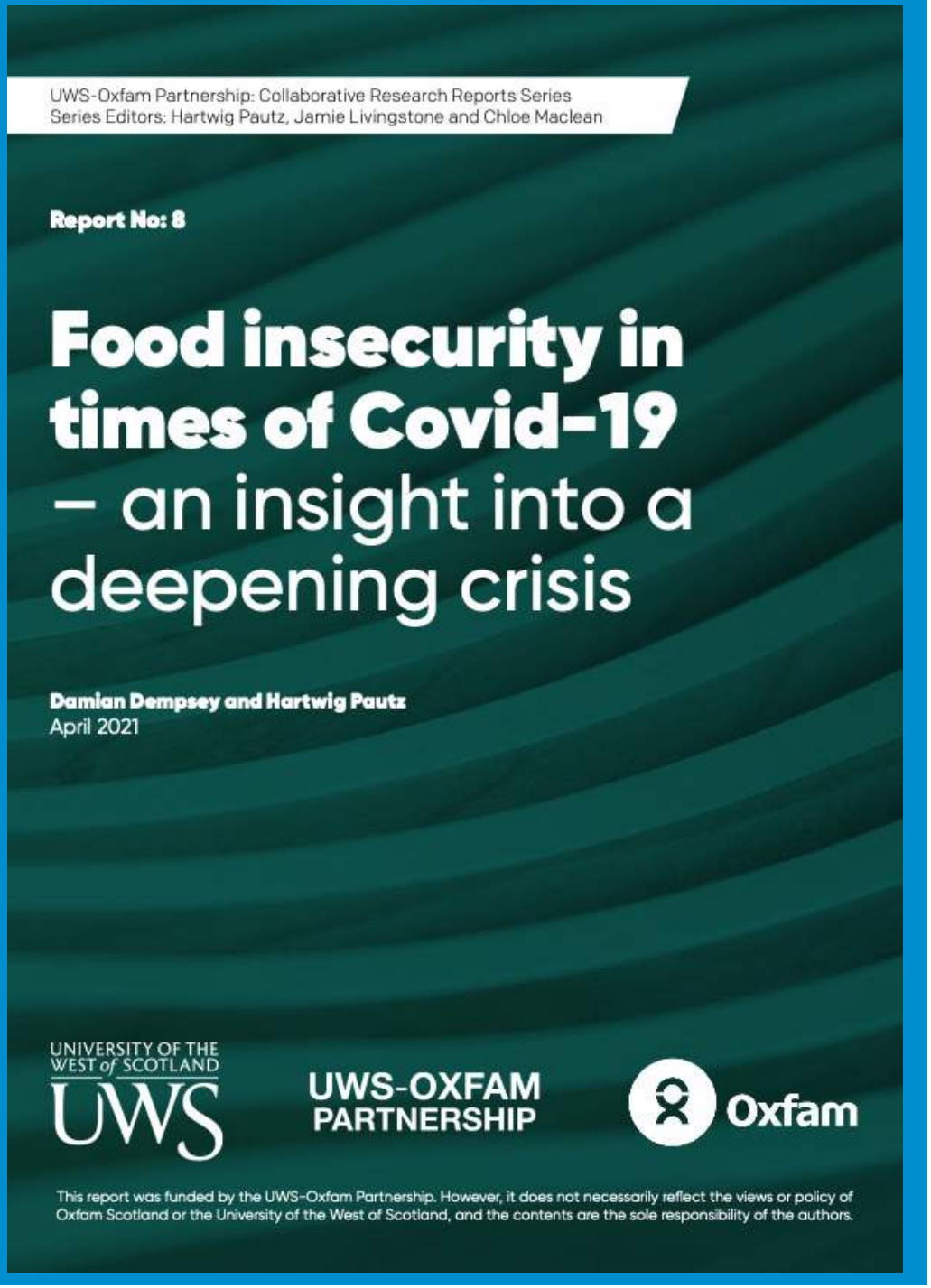
Increasing food insecurity in UK

& food poverty issue in children not attending school

high profile campaign to secure meals for children in receipt of free school meals when schools were closed

April 2021 report - food insecurity in UK is increasing

Increasing numbers of people replying on food banks



Trussell Trust Data

From report on previous page

	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20
UK	913,982	1,091,282	1,112,395	1,201,302	1,354,388	1,606,244	1,900,122
Scotland	72,487	119,212	135,943	150,095	173,526	217,006	237,225

Table 1: Number of Trussell Trust foodbank parcels handed out by year (The Trussell Trust 2020a)

2020 Inequality In UK Food System

“increased unemployment, reduced hours, and enforced self-isolation for multiple vulnerable groups is likely to lead to an increase in UK food insecurity, exacerbating diet-related health inequalities. The social and economic crisis associated with the pandemic has exposed the fragility of the system of food charity which, at present, is a key response to growing poverty. A vulnerable food system, with just-in-time supply chains, has been challenged by stockpiling.”

Emerald Open Research

Emerald Open Research 2020, 2:11 Last updated: 28 APR 2020

Check for updates

OPINION ARTICLE

How Covid-19 has exposed inequalities in the UK food system: The case of UK food and poverty [version 1; peer review: 3 approved, 2 approved with reservations]

Madeleine Power[1], Bob Doherty[2], Katie Pybus[1], Kate Pickett[1]

[1]Health Sciences, University of York, York, Yorkshire, YO10 5GD, UK
[2]The York Management School, University of York, York, Yorkshire, YO10 5GD, UK

v1 **First published:** 03 Apr 2020, **2**:11
https://doi.org/10.35241/emeraldopenres.13539.1
Latest published: 03 Apr 2020, **2**:11
https://doi.org/10.35241/emeraldopenres.13539.1

Abstract

This article draws upon our unique perspective as academic-practitioners working in the fields of food insecurity, food systems, and inequality to comment on the empirical and ethical implications of Covid-19 for socio-economic inequalities in access to food in the UK. The Covid-19 pandemic has revealed the profound insecurity of large segments of the UK population; increased unemployment, reduced hours, and enforced self-isolation for multiple vulnerable groups is likely to lead to an increase in UK food insecurity, exacerbating diet-related health inequalities. The social and economic crisis associated with the pandemic has exposed the fragility of the system of food charity which, at present, is a key response to growing poverty. A vulnerable food system, with just-in-time supply chains, has been challenged by stockpiling. Resultant food supply issues at food banks, alongside rapidly increasing demand and reduced volunteer numbers, has undermined many food charities, especially independent food banks. In the light of this analysis, we make a series of recommendations for social security policy, ‘emergency’ food provision, and retailers. We call for an immediate end to the five week wait for Universal Credit and cash grants for low income households. We ask central and local government to recognise that many food aid providers are already at capacity and unable to adopt additional responsibilities. We urge supermarkets to commit to paying their employees the Real Living Wage to mitigate against food insecurity amongst their staff now and in the future. The government's -- impressive -- response to the economic crisis associated with Covid-19 has underscored a key principle: it is the government's responsibility to protect population health, to guarantee household incomes, and to safeguard the economy. Millions of households were in poverty before the pandemic, and millions more will be so unless the government continues to protect household incomes through policy change.

Keywords

food insecurity, food banks, food supply, inequality, poverty, Covid-19, coronavirus, pandemic

Open Peer Review

Reviewer Status ? ? ✓ ✓ ✓

	Invited Reviewers				
	1	**2**	**3**	**4**	**5**
version 1 03 Apr 2020	? report	? report	✓ report	✓ report	✓ report

1 **Peter Jackson**, University of Sheffield, Sheffield, UK

2 **Rachel Loopstra**, King's College London, London, UK

3 **Alex Murdock**, London South Bank University, London, UK

4 **Diane Holt**, University of Leeds, Leeds, UK

5 **Andrew Williams**, Cardiff University, Cardiff, UK

Any reports and responses or comments on the article can be found at the end of the article.

Nutrition advice & wider accessibility

A lot of nutritional info (social media) may seem of reach for those on benefits…

Fresh fruits, meat, fish and veggies perceived as expensive and perishable by those on low incomes

Their focus might be on foods to stave off hunger and foods that last: carbohydrates, bread, pasta, tinned long-life produce.

I'd like to see more nutrition advice using *very* basic cheap ingredients (frozen fruits/veg if needs be, eggs, beans and professionals aware of budget shops and ingredients)

Why important re COVID-19?

European Journal of Clinical Nutrition
https://doi.org/10.1038/s41430-020-0634-3

PERSPECTIVE

Nutrition amid the COVID-19 pandemic: a multi-level framework for action

Farah Naja[1] · Rena Hamadeh[1]

Received: 24 March 2020 / Revised: 1 April 2020 / Accepted: 1 April 2020

COVID-19, a disease caused by a novel coronavirus, became a major global human threat that has turned into a pandemic. Coronavirus is one of the major pathogens that mainly targets the human respiratory system. In late December 2019, a cluster of patients were admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology [1]. Early reports predicted the onset of a possible coronavirus outbreak called SARS-CoV-2, causing the disease COVID-19. The ongoing epidemic has been declared by the World Health Organization (WHO) as a global public health emergency [2].

Experiences from previous outbreaks have shown that as an epidemic evolves, there is an urgent need to expand public health activities beyond direct clinical management and extend to cover basic principles of management and optimization of resource utilization [3]. Since the outbreak of the COVID-19, individual and community resilience emerged as a main resource while remaining the first line of defense in emergency preparedness. In fact, psychological and behavioral countermeasures of both the individual and the community are vital determinants to improve resilience and enhance the efficacy of public health approaches vis a vis a pandemic of a magnitude similar to that of COVID-19 [4]. The nutritional status of individuals has for long been considered as an indicator of resilience against destabilization [5]. The ecology of adversity and resilience demonstrates that substantial stressors, such as inadequate nutrition, can lead to long-lasting effects that are linked to health [6]. In fact, poor diet quality has been associated not only with physical but also mental health [7]. Optimal nutrition and dietary intake is a resource that transcends the individual, the community to reach global influence [8].

✉ Farah Naja
fn14@aub.edu.lb

[1] Department of Nutrition and Food Sciences, American University of Beirut, Beirut, Lebanon

Published online: 30 April 2020

In order to enhance the physical and mental health of individuals vis a vis the COVID-19 pandemic, this commentary presents a framework for action to maintain optimal nutrition at the individual, community, national and global levels using an adapted version of the ecological model of health behavior (Fig. 1).

At the individual level, the common denominator that drives most of the nutrition and dietary recommendations to combat viral infections, including COVID-19, lies within the link between diet and immunity. In fact, existing evidence highlights that diet has a profound effect on people's immune system and disease susceptibility. It has been demonstrated that specific nutrients or nutrient combinations may affect the immune system through the activation of cells, modification in the production of signaling molecules, and gene expression [9]. Furthermore, dietary ingredients are significant determinants of gut microbial composition and consequently can shape the characteristics of immune responses in the body [10]. Nutritional deficiencies of energy, protein, and specific micronutrients are associated with depressed immune function and increased susceptibility to infection. An adequate intake of iron, zinc, and vitamins A, E, B6, and B12 is predominantly vital for the maintenance of immune function [11]. Therefore, the key to maintaining an effective immune system is to avoid deficiencies of the nutrients that play an essential role in immune cell triggering, interaction, differentiation, or functional expression.

COVID-19 world pandemic imposed a new set of challenges for the individual to maintain a healthy diet. First, the state of lockdown announced in many countries around the globe led all public and private sector institutions, with the exception of health care facilities and a limited number of essential services, to close down and, if possible, carry its operations remotely (without face to face interactions). Individuals were asked to stay home and avoid contact with other people [12]. Such measures of self-isolation and social distancing are known to be crucial in limiting the spread of the virus, flattening the curve of incidence rate, and

"The nutritional status of individuals has long been considered an indicator of resilience against destabilization….and inadequate nutrition can lead to long-lasting effects that are linked to health. In fact poor diet quality has been associated with not only poor physical health but also mental health."

Assessing Malnutrition?

The National Institute for Health and Clinical Excellence (NICE) in UK has recommended for some time that nutritional screening tools such as MUST (Malnutrition Universal Screening Tool) be used on patients admitted to hospital (NICE, 2006).

MUST is a five-step tool developed by British Association for Parenteral and Enteral Nutrition (BAPEN).

Information and materials are available at:-
www.bapen.org.uk Dietetic practice

MUST

Should be undertaken weekly after hospital admission but can also be used in a community setting.

Uses BMI and weight loss as the primary determinants of risk; hence may not be able to identify obese or overweight individuals with micronutrient deficiencies.

Data on completion of nutritional assessment has been reported before the pandemic, a cross-sectional study in one hospital reported suboptimal completion of MUST (Dingwal et al 2012).

References to follow in a few slides

Pre Covid data on MUST

In the Dingwal et al 2012 study, ten patients were randomly selected from ten wards across the hospital (100 patients in total).

No wards had 100% completion of MUST assessments, whilst eight of ten of the wards had nutritional care plans, 45% of the 100 patients did not have a MUST score.

Of the patients that did have a MUST score, 52% were found to be at a medium or high risk of nutritional deficiency.

How well is MUST completed?

Middleton et al (2012) reported 'high' levels of completion (but below the target level of 100%) but also state rates of completion drops off over the period of 4 weeks after admission 87% completion reported in week one, 89% in week two, 85% in week three and 84% in week four.

Another study reports similarly that the MUST tool was under-utilised on vascular wards, but the authors did state that usage of the tool increased following education (Tewari et al 2013).

Accuracy of completion needs to be considered too (Smith 2014).

References

Dingwal S, Shah S, Patel A et al PMO-037 Adult nutritional status assessment in a hospital: cross sectional study in a UK hospital. *Gut* 2012 61(Suppl 2):A88–A89

Middleton J, Farnsworth H, Singh G PMO-034 Compliance with the must screening tool for medical in patients. *Gut* 2012 61: A87

Smith A Potential barriers to effective MUST implementation. *British Journal of Community Nursing* 2014 19: Sup11, S28–S31

Tewari N, Rodrigues J, Bothamley L et al The utilisation of the MUST nutritional screening tool on vascular surgical wards. *BMJ Open Quality* 2013 2(1): pii: u201374.w1122

How other countries assess?

BMI based approach used in studies on Covid in France

- Severe malnutrition weight loss > 10% than before COVID-19 or a BMI < 17 (70 years old).
- Moderate malnutrition was defined as weight loss > 5% than before COVID-19 or BMI < 18.5 (< 21 for patients > 70 years old)

HAS HAdS. Diagnostic de la dénutrition de l'enfant et de l'adulte. Saint-Denis La Plaine. 2019.

Thibault R, Quilliot D, Seguin P, Tamion F, Schneider S, Déchelotte P. Nutritional care at hospital during the Covid-19 viral epidemic: Expert opinion from the French-speaking Society for Clinical Nutrition and Metabolism (SFNCM). Nut Clin et Métab. 2020;34:97-104

Review of 14 studies on nutritional assessment in Covid -19 concludes of risk of deficiency in older males with co-morbidities

International Journal of
Environmental Research and Public Health

MDPI

Review

Approaches to Nutritional Screening in Patients with Coronavirus Disease 2019 (COVID-19)

Amira Mohammed Ali [1,2,*] and Hiroshi Kunugi [1,3]

[1] National Center of Neurology and Psychiatry, Department of Mental Disorder Research, National Institute of Neuroscience, Tokyo 187-0031, Japan; hkunugi@ncnp.go.jp
[2] Department of Psychiatric Nursing and Mental Health, Faculty of Nursing, Alexandria University, Alexandria 21527, Egypt
[3] Department of Psychiatry, Teikyo University School of Medicine, Tokyo 173-8605, Japan
* Correspondence: mercy.ofheaven2000@gmail.com; Tel.: +81-042-346-1714

Abstract: Malnutrition is common among severe patients with coronavirus disease 2019 (COVID-19), mainly elderly adults and patients with comorbidities. It is also associated with atypical presentation of the disease. Despite the possible contribution of malnutrition to the acquisition and severity of COVID-19, it is not clear which nutritional screening measures may best diagnose malnutrition in these patients at early stages. This is of crucial importance given the urgency and rapid progression of the disease in vulnerable groups. Accordingly, this review examines the available literature for different nutritional screening approaches implemented among COVID-19 patients, with a special focus on elderly adults. After a literature search, we selected and scrutinized 14 studies assessing malnutrition among COVID-19 patients. The Nutrition Risk Screening 2002 (NRS-2002) has demonstrated superior sensitivity to other traditional screening measures. The controlling nutritional status (CONUT) score, which comprises serum albumin level, cholesterol level, and lymphocytes count, as well as a combined CONUT-lactate dehydrogenase-C-reactive protein score expressed a predictive capacity even superior to that of NRS-2002 (0.81% and 0.92% vs. 0.79%) in midlife and elder COVID-19 patients. Therefore, simple measures based on routinely conducted laboratory investigations such as the CONUT score may be timely, cheap, and valuable alternatives for identifying COVID-19 patients with high nutritional risk. Mini Nutritional Assessment (MNA) was the only measure used to detect residual malnutrition and high malnutrition risk in remitting patients—MNA scores correlated with hypoalbuminemia, hypercytokinemia, and weight loss. Older males with severe inflammation, gastrointestinal symptoms, and pre-existing comorbidities (diabetes, obesity, or hypertension) are more prone to malnutrition and subsequently poor COVID-19 prognosis both during the acute phase and during convalescence. Thus, they are in need of frequent nutritional monitoring and support while detecting and treating malnutrition in the general public might be necessary to increase resilience against COVID-19.

Keywords: coronavirus disease 2019/COVID-19; cytokine storm; older adults/elderly; aging/age-related non-communicable diseases; malnutrition/nutritional deficiencies; Nutrition Risk Screening 2002; the controlling nutritional status score/CONUT score; anemia/ferritin; vitamin D; selenium; micronutrients

Citation: Ali, A.M.; Kunugi, H. Approaches to Nutritional Screening in Patients with Coronavirus Disease 2019 (COVID-19). *Int. J. Environ. Res. Public Health* **2021**, *18*, 2772. https://doi.org/10.3390/ijerph18052772

Academic Editors: Riccardo Polosa, Pietro Ferrara, Luciana Albano and Venera Tomaselli

Received: 4 January 2021
Accepted: 2 March 2021
Published: 9 March 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Overview

Coronavirus disease 2019 (COVID-19) is a highly infectious viral disease that results from pulmonary invasion by a beta-coronavirus, known as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [1]. Even though the disease is asymptomatic in most patients, symptoms of cough, dyspnea, unremitting fever, myalgia, and fatigue commonly occur in specific patient groups; mainly elderly adults and people with chronic disorders such as diabetes mellitus, cardiovascular disorders, obesity, and cancer [2–4]. SARS-CoV-2 induces serious adverse effects in these groups including acute respiratory

Different methods of assessment considered

"The Nutrition Risk Screening 2002 (NRS-2002) has demonstrated superior sensitivity to other traditional screening measures. The controlling nutritional status (CONUT) score, which comprises serum albumin level, cholesterol level, and lymphocytes count, as well as a combined CONUT-lactate dehydrogenase-C-reactive protein score expressed a predictive capacity even superior to that of NRS-2002 (0.81% and 0.92% vs. 0.79%) in midlife and elder COVID-19 patients. Therefore, simple measures based on routinely conducted laboratory investigations such as the CONUT score may be timely, cheap, and valuable alternatives for identifying COVID-19 patients with high nutritional risk. Mini Nutritional Assessment (MNA) was the only measure used to detect residual malnutrition and high malnutrition risk in remitting patients".

from previous paper

"MNA scores correlated with hypoalbuminemia, hypercytokinemia, and weight loss. Older males with severe inflammation, gastrointestinal symptoms, and pre-existing comorbidities (diabetes, obesity, or hypertension) are more prone to malnutrition and subsequently poor COVID-19 prognosis both during the acute phase and during convalescence. Thus, they are in need of frequent nutritional monitoring and support while detecting and treating malnutrition in the general public might be necessary to increase resilience against COVID-19".

from previous paper

Our review: Key Micronutrients

B, C, E, Fe, Se, Zinc Vit D, stress, & microbiome

Later look in more detail at latest research on Vit D as more published since

complications and re-admission after discharge (4). Malnutrition can occur in both energy and macronutrient terms (carbohydrates, proteins, fats) and may also occur as micronutrient (vitamins and minerals) deficiency, which can potentially co-exist with obesity, where someone is potentially overfed in terms of energy (Kcal) but deficient in one or more micronutrients. A study published in 2017 reported on data from 1990-2017 and concluded that dietary factors were linked to 11 million deaths and 255 million disability-adjusted life-years across the world in 2017 (5).

Any infection outcome is affected by nutritional status, due to effects on both innate and adaptive immune responses (6). Vitamins B, C, and E alongside iron, selenium, and zinc play a supporting role in immunocompetence (7, 8), and any chronic shortages in these micronutrients may further impair immune function through cell activation and changes in signaling, molecule production, and gene expression (9). It should also be remembered that diet (and particularly components such as fiber) influences gut microbial composition which helps to promote immune responses in the body (10).

Vitamin D Status

Vitamin D may protect against the risk of contracting influenza (11), and vitamin D deficiency is associated with a higher risk of community-acquired pneumonia (12) and GI disorders such as inflammatory bowel disease (13). It also seems to be an important factor in other viral respiratory infections. Alipio (14) presented significant data ($p<0.001$) regarding vitamin D status and the severity of SARS symptoms observed in patients admitted to three hospitals in South Asia. The data indicated that the majority of patients with mild symptoms (n=85.5%) presented with serum OH(D) of 31.2 ng/mmol (normal vitamin D status), with only 3.6% of patients in this category presenting with severe and critical symptoms (14).

Vitamin D deficiency is common in people who are housebound and not going outside as vitamin D is synthesized through skin exposure to sunlight. Thus, a population in quarantine or lockdown may experience lowered levels of vitamin D. Moreover, skin pigmentation also affects production levels; skin with more pigmentation will produce less, so deficiency is more common in people with darker skin (15). Debates about whether this is implicated in higher death rates from COVID-19 infection among Black, Asian, and minority ethnic people (16) are gaining momentum. Both obesity and Type 2 diabetes (T2D) are also associated with high rates of vitamin D deficiency (17). It is also known that people with diabetes and obesity are more vulnerable to severe disease with COVID-19 infection. It seems vitamin D deficiency is relatively commonplace, as over a billion people globally are thought to be affected (18). In the UK, a country with high COVID-19 death rates, around a third of adults appear to be deficient in vitamin D. The National Diet and Nutrition Survey analysis of the last 9 years reported that in the UK from January to March, 19% of children aged 4 to 10 years, 37% of children aged 11 to 18 years, and 29% of adults had low Vitamin D levels (25-OHD below 25nmol/L), indicating a risk of deficiency (19).

Stress

Physical trauma is known to cause injury and dysfunction of the gut as well as increased intestinal permeability (20). Psychological stress also impacts gut dysbiosis and permeability by increasing the corticotropin-releasing hormone and its effect on TNFα (21), as well as other pro-inflammatory cytokines, which is evident in viral infections. The effect of being critically ill may compound an already compromised GI tract, and it is known that gut dysfunction can contribute to multi-organ dysfunction syndrome (20). Other GI mechanisms relevant to the pathophysiology of viral infection include the reduction of butyrate, which helps to maintain the gut barrier and is known for its anti-inflammatory effects, and the elevation of circulating lipopolysaccharides from the increase in gut permeability (22). This leads to the upregulation of inflammatory cytokines, which triggers systemic inflammation (23, 24). The consequential impact on mitochondrial function together with immune system responses further demonstrate the potential effects of COVID-19 on a range of interconnected body systems (25).

Microbiome and Immunity

Gut microbiota influences the maturation and development of immune cells such as dendritic cells and T cells, while also regulating the synthesis of the

In Critical Illness

The effect of being critically ill may compound an already compromised GI tract and it is known that gut dysfunction can contribution to multi organ dysfunction syndrome (MODS).

ICU stays and not eating = risk of nutritional deficiency – requiring dietetic management and specialist support/ enteral/ TPN feeding.

Dietetic and consultant management of TPN =Total parenteral nutrition (which passes GI tract) or enteral via GI tract (e.g. naso-gastric tube)

What else makes people vulnerable to infection & inflammation?

Physical trauma is known to cause injury to the gut and dysfunction as well as increasing intestinal permeability.

Psychological stress also impacts gut dysbiosis and permeability through the increase of corticotropin releasing hormone (CRH) and its effect on TNFa, as well as other proinflammatory cytokines, which are evident in viral infections.

Protein turnover in early response to Covid-19

- This is increased in critical illness.
  - Mechanisms may include muscle invasion by virus particles and immune-mediated muscle injury, BUT proof of SARS-CoV-2 invading muscle cells is lacking.
- There's a condition called critical illness myopathy – which is muscle deconditioning due to immobility important in terms of rehabilitation.
  - Remember vitamin D is also important for muscle condition.
- Protein needs in a cytokine storm?

Why is GI tract important in terms of immunity?

Gut permeability upregulates inflammatory cytokines and this can trigger systemic inflammation.

Butyrate helps to maintain gut barrier and it has been suggested from animal studies that that butyrate could suppress viral infectivity by decreasing membrane ACE2, via downregulating its transcription and increasing its shedding and decreasing activation of viral spike protein.

Jing Li Elaine M. Richards Eileen M. Handberg Carl J. Pepine Mohan K. Raizada Butyrate Regulates COVID-19–Relevant Genes in Gut Epithelial Organoids From Normotensive Rats Hypertension. 2 Dec 2020 https://doi.org/10.1161/HYPERTENSIONAHA.120.16647 2021;77:e13–e16

Our review: Obesity

Risk factor for severe disease, ICU stays, increased mortality metabolic dysfunction, inflammation

High levels of ACE2 expressing cells are in adipose tissue

- ACE2 receptor significant re viral entry

secreting cells (42) and T-cell proliferation (43), respectively.

Obesity as a Risk Factor for Severe Disease in COVID-19

Obesity has been identified by the World Health Organization as a serious risk factor for COVID-19 outcomes and for poor adverse outcomes for COVID-19 (44). Increasing risks have been associated with increasing BMI (45). In a New York hospital cohort study (n=3615), obesity was cited as a risk factor for treatment escalation (46) and for admission to intensive care units (ICU) in the United Kingdom (UK). A study by the UK Intensive Care National Audit and Research Centre reported that over 73% of those in ICUs were overweight or obese (34.6% and 38.5%, respectively) (47). Obesity was recognized as a risk factor for in-hospital mortality after adjusting for other comorbidities in an observational, prospective cohort study in the UK (n=16,749) (48).

Although obesity is associated with severe forms of COVID-19, the prevalence of severe obesity (BMI >35kg/m^2) reported in ICUs may reflect the local prevalence of obesity as seen in two seminal studies in France, one in Lille, where the local prevalence was reported as 28.2% (45), and one in Lyon, where the prevalence was 11.3%. The requirement for invasive mechanical ventilation (IMV) compared to lean subjects reflected these differences with 68.6% and 58.4%, respectively. In a retrospective cohort study, obesity prevalence was high among ICU patients (44), and in other research, patients with a BMI between 30-34.9kg/m^2 were 1.8 times more likely than those with a BMI <30kg/m^2 to be admitted to the ICU (46). This is more of an issue in the USA and UK (countries which have high mortality rates in the current pandemic) because of the high prevalence of obesity (42% and 29%, respectively) (49, 50)

Obesity is a risk factor for impaired metabolic function, such as insulin resistance and T2D (51). The metabolic effect of excessive fat may result in reduced pancreatic beta cell performance, which may be compounded by the direct effect of COVID-19 on function (52). Inflammation of adipose tissue results in other metabolic dysfunctions such as dyslipidemia, hypertension, and cardiovascular disease (CVD) (51, 53). Although comorbidities for obesity such as heart and lung disease, hypertension, and T2D may confound results, severe obesity has been associated with ICU admissions and obesity associated with the use of IMV (both reaching statistical significance) (54).

Obesity and Immune Function

Obesity may predispose adults to impaired immune function and increased susceptibility to infection (51). Multiple factors are implicated, such as chronic inflammatory status, delayed immune response, and the complex relationships and interactions between adipose tissue and the immune system (55). High levels of ACE2-expressing cells are found in adipose tissue, and because obese individuals have more adipose tissue, this could elucidate that they have a greater amount of ACE2. COVID-19 has an enhanced affinity for ACE2 (53), which is a supposed receptor for the entry of COVID-19 into host cells (56).

Adipose tissue may contribute to the progression of COVID-19 by other mechanisms, including the imbalance between anti-and pro-inflammatory cytokines, particularly adipokines; overexpression of the latter may lead to aberrant chemotaxis and abnormal macrophage differentiation, further compromising immune function (55). Other innate responses associated with obesity lead to the excessive release of pro-inflammatory cytokines such as IL-6 (55), TNFα, IFNγ, and IL-2 and higher levels of circulating C-reactive protein (53). Elevated IL-6 levels have been correlated with ICU admission, respiratory failure, and adverse outcomes (39).

Obesity and the Microbiota

Studies have shown that obesity is associated with changes in the assortment of microorganisms inhabiting the GI tract, which include viral, fungal, bacterial, and single-celled microorganisms called arcaea, collectively known as the gut microbiota, and that obese adults have less diversity and richness in the bacterial composition (57-59). As previously mentioned, gut bacteria play a vital role in protection against pathogenic microorganisms, immune modulation, and other functions such as digestion and metabolism and SCFA production (60-62).

Firmicutes and Bacteroidetes make up approximately 90% of the total microorganisms with some research reporting an increased ratio of *Firmicutes* to *Bacteroidetes* in the feces of obese subjects (57, 63,

Our review: obesity and eating habits

Explored microbiome and links to inflammation

Nutritional support to include fiber for microbiome / satiety, fermented foods as source of probiotics and tryptophan for melatonin synthesis

Role of healthy lifestyles, prevention, multi-disciplinary team working

64); however, a systematic review was equivocal in its overview of the association between BMI and microbiota (65) with some studies supporting this theory and others finding no association, although this may be explained by differing methodological approaches.

Recent evidence suggests the presence of microorganisms such as *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* in the lungs and that a bidirectional relationship exists between the lungs and the gut (66). Dysbiosis, which results from a lack of gut diversity, has been associated with many diseases, including acute respiratory distress syndrome and sepsis (67).

2.4. Obesity and Dietary Habits

Obesity is affected by unhealthy eating habits, as seen in a cross-sectional study (n=1557) that looked at the association of abdominal obesity with food inadequacy and physical activity (68). They reported a lower likelihood of abdominal adiposity in those who consumed a minimum of three portions of fruit a day and did not exceed the upper limit of saturated fat (35% and 28%, respectively). Furthermore, in data from a longitudinal study n=50, improvements were found in weight, body fat, and waist circumference on a diet of fruits, vegetables, and grains containing 30g fiber/day compared to controls (69). Normal weight adults (n=52) consumed 43% more complex carbohydrates and 33% more fiber than overweight/obese adults when matched for gender, age, and physical activity (77).

Diets that include high fat and low fiber can impact the diversity of the human gut microbiota, even over a few days (70). Conversely, a fiber-rich diet may have a positive effect on the gut microbiota and improve both metabolic and immune markers; for example, non-digestible carbohydrates such as whole grains may reduce pro-inflammatory cytokine IL-6 and insulin resistance (71). Interestingly, switching from a Western style diet of high fat/high sugar refined carbohydrates to a low-fat diet rich in plant-polysaccharides may influence the composition of microbiota, once again within a relatively short time, this time to the benefit of the microbiota (42). In addition, probiotics found in fermented foods may further reduce inflammation and help to regulate innate immunity (72). Anti-inflammatory marker IL-10 may be increased through the intake of prebiotics, increasing the production of SCFAs and improving the health of the GI-associated lymphoid tissue. Not only gut microbiota, but also lung microbiota is improved, thus offering a potential strategy for improving clinical outcomes of COVID-19 (41).

Melatonin

Melatonin, released by the pineal gland at nighttime, has long been associated with the adjustment of the circadian phase to the environment, known as circadian rhythm entrainment; however, it also has antioxidant and anti-inflammatory properties, the latter due to its close relationship with mitochondrial function (73). The melatonergic pathway, which starts with the conversion of tryptophan to serotonin, then to N-acetylserotonin, and finally to melatonin, has created some interest due to its interaction with COVID-19 and other viruses (25). Elevated levels of stress may affect the availability of tryptophan for the melatonergic pathway, thus causing circadian (74, 75) and mitochondrial dysregulation (76). Pre-existing medical conditions mentioned previously have been linked to both of these regulatory mechanisms as well as to gut dysbiosis and increased gut permeability.

Supportive Nutritional Interventions

Multidisciplinary Team Practice

This review has indicated clear links between nutrition status (specifically micronutrient insufficiency and deficiency), compromised gut function, and the effects of obesity on viral severity, including SARS, CAP, and now COVID-19. Hence, a multidisciplinary approach is likely to be of benefit in terms of patient outcomes.

Health services should adapt to prioritize reducing obesity and weight loss in general, given the inverse correlation between obesity/excess weight and COVID-19 severity. In response to this, the UK government launched an obesity strategy, labeled the COVID-19 'wake-up-call', in July 2020 (81). The preventative strategies outlined include general practitioners being incentivized to prescribe activity and exercise to enhance physical fitness and primary care healthcare staff being trained as 'healthy weight coaches' to provide more specialist support to those in need (81).

Allied health professionals with nutrition expertise such as dieticians, nutritionists, and nutritional therapists may also have a role in supporting individuals in their recovery from COVID-19 or in advising those seeking preventative or 'prehabilitation' healthy eating advice

Remember microbiome's wider impacts

Microbiome influences

- Immunity
- Inflammation
- Absorption & nutritional status
- Hormones
- Metabolism
- Detoxification

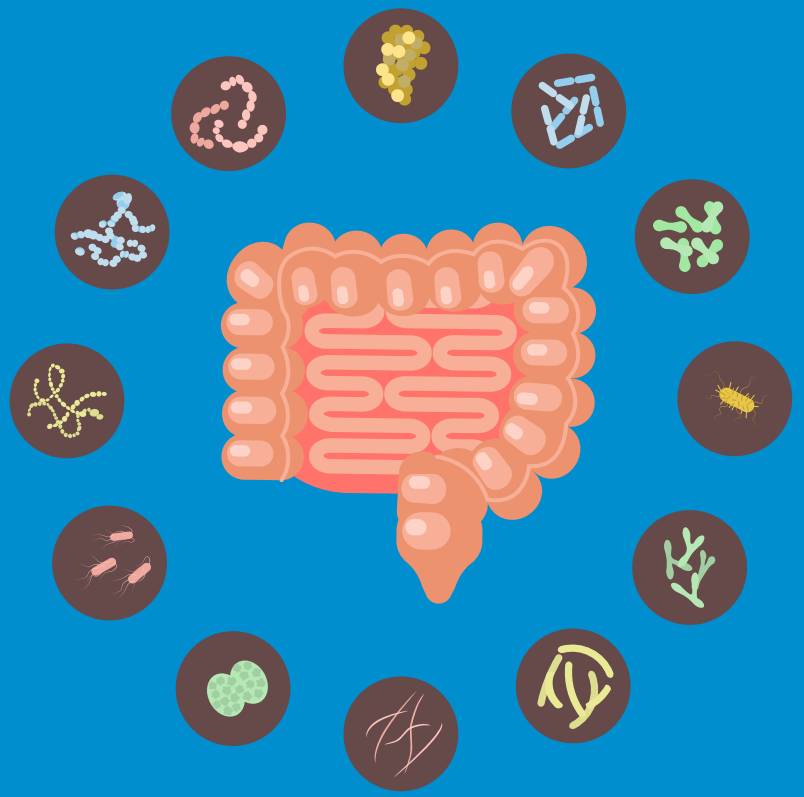


Image: digestive tract and probiotics istock

Effects of Covid-19 on physical act of eating & digestive system

- Anosmia – partial or complete loss of sense of smell
- Dysgeusia – distortion of sense of taste
- Diarrhea – dehydration risk
- Dyspnea – shortness of breath can affect eating
- Asthenia – physical weakness can affect eating
- Food aversion – can reduce food intake

Consequences of Olfactory and gustatory dysfunction in Covid-19

Anosmia maybe associated with less food/calorie intake.

Anosmia has also been reported as protective against severe disease in Covid -19 with less need for oxygen therapy in patients with anosmia

Vacchiano V, Riguzzi P, Volpi L, Tappata M, Avoni P, Rizzo G, et al. Early neurological manifestations of hospitalized COVID-19 patients. Neurol Sci. 2020;41:2029-31.

Consequences of Olfactory and gustatory dysfunction in Covid-19

Anosmia was associated with milder forms of Covid-19 in patients who did not require hospitalisation.

Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory lossassociates with outpatient clinical course in COVID-19. Int Forum Allergy Rhinol. 2020;10:821-

Alteration of taste perception may also contribute to weight loss in many other diseases

Roos DS, Oranje OJM, Freriksen AFD, Berendse HW, Boesveldt S. Flavor perception and the risk of malnutrition in patients with Parkinson's disease. J Neural Transm (Vienna). 2018;125:925-30.

Sarcopenia

Proposed as part of the definition of malnutrition (Jensen et al., 2019)

Jensen GL, Cederholm T, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM Criteria for the Diagnosis of Malnutrition: A Consensus Report From the Global Clinical Nutrition Community. JPEN J Parenter Enteral Nutr. 2019;43:32-40.

Sarcopenic obesity is the co-existence of low muscle mass and obesity

Davis C. The Gut Microbiome and Its Role in Obesity. Nutr Today 2016;51:167-74.

Associated with inflammation (as a result of excess adipose tissue) and compromised functioning of antibody secreting cells and T cell proliferation

Our review: Recommendations

Table 1. Recommended intakes of vitamins D and C to support optimal immunity for the wider population.

Nutrient	Justification	Recommendation
Vitamin D	Revision of the current UK guidelines is advocated (82). 10 µg/d is not sufficient for individuals in at-risk groups at any time (82). 10 µg/d is not sufficient for individuals between October-April in cold, Northern Hemisphere countries (77).	Daily intake of 50 µg/d (84, 85) [Daily intake of 50-125 µg/d has been advised dependent on age, risk, and time of year (11).]
Vitamin C	40 mg/d is not sufficient for UK adults (86). EU guidance for adults is 95 mg/d (87). Higher daily doses (≥200mg/d) are required for optimal immune function (84).	Daily intake of 200 mg/d (84) [Daily intake of 1-2 g/d for individuals who are unwell (84)]

Gastroenterol Hepatol Bed Bench 2020;13(4):331-340

Adults – general population

Vit D 50ug/day

Vit C 200 mg/day or 1-2g/day if unwell

This is above what is in current UK guidelines

2021 Systematic Review on Vitamin D and Covid-19

39 studies: qualitative synthesis. Studies so far have been heterogeneous in their design both in terms of methodology and statistics.

BUT most indicated a significant relationship between 25(OH)D and SARS-CoV-2 infection, disease severity and mortality.

Kazemi A, Mohammadi V, Aghababaee SK, Golzarand M, Clark CCT, Babajafari S. Association of Vitamin D Status with SARS-CoV-2 Infection or COVID-19 Severity: A Systematic Review and Meta-analysis. Adv Nutr. 2021.

Types of studies

Cohort, retrospective cohort, cross sectional, 1x RCT, 2x quasi experimental case- controlled, retrospective observational, prospective multi-center observational

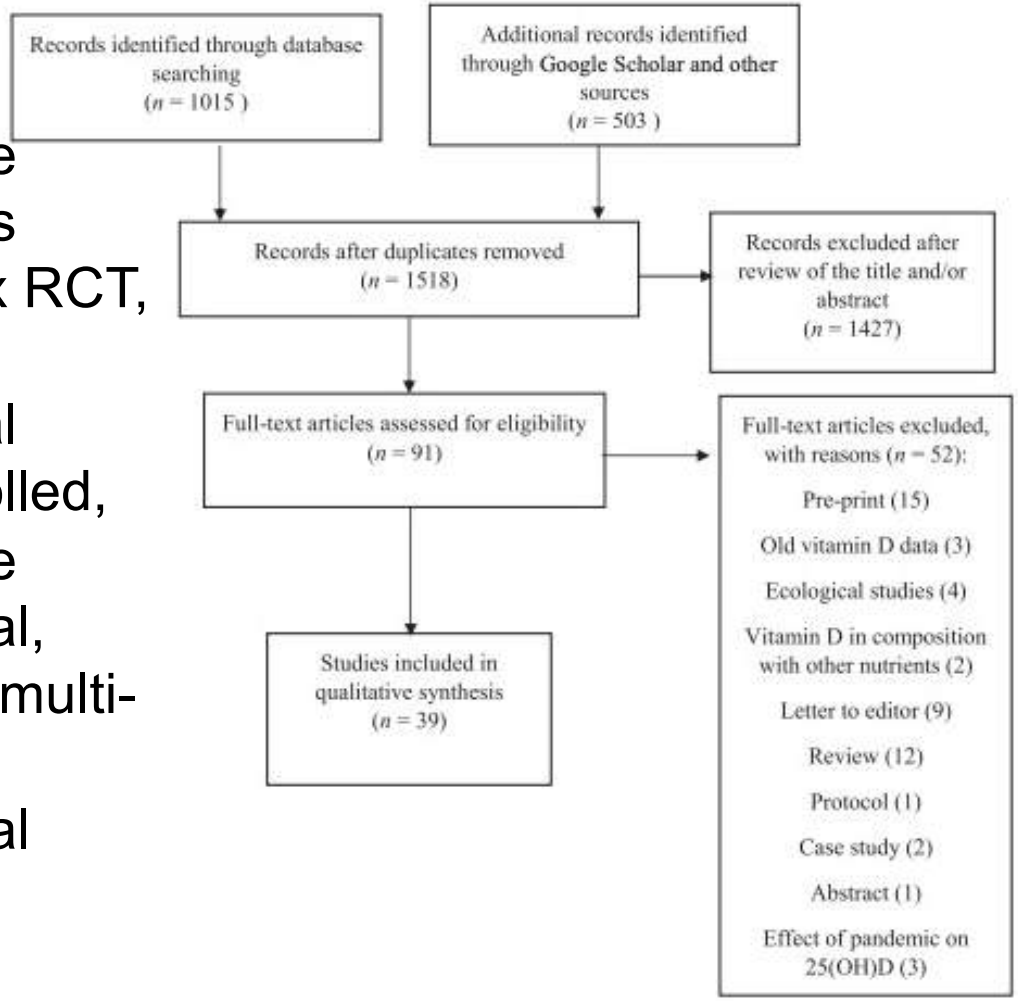


FIGURE 1 Summary of the process for selecting studies that investigated the association of vitamin D status with SARS-CoV-2 infection and COVID-19 severity. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 25(OH)D, 25-hydroxyvitamin-D.

PRISMA diagram from this review

"All retrospective and prospective cohort, cross-sectional, case-control, and randomized controlled trial studies that investigated the relation between 25(OH)D and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 severity were included. Thirty-nine studies were included in the current systematic review. In studies that were adjusted (OR: 1.77; 95% CI: 1.24, 2.53; *I*2: 44.2%) and nonadjusted for confounders (OR: 1.75; 95% CI: 1.44, 2.13; *I*2: 33.0%) there was a higher risk of SARS-CoV-2 infection in the vitamin D deficiency (VDD) group. Fifteen studies evaluated associations between VDD and composite severity. In the studies that were adjusted (OR: 2.57; 95% CI: 1.65, 4.01; *I*2 = 0.0%) and nonadjusted for confounders (OR: 10.61; 95% CI: 2.07, 54.23; *I*2 = 90.8%) there was a higher severity in the VDD group. Analysis of studies with crude OR (OR: 2.62; 95% CI: 1.13, 6.05; *I*2: 47.9%), and adjusted studies that used the Cox survival method (HR: 2.35; 95% CI: 1.22, 4.52; *I*2: 84%) indicated a significant association of VDD with mortality, while in adjusted studies that used logistic regression, no relation was observed (OR: 1.05; 95% CI: 0.63, 1.75; *I*2: 76.6%)."

from previous paper

TABLE 1 Characteristics of studies investigated association of vitamin D status with SARS-CoV-2 infection[1]

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Definition of VitD deficiency	Time of VitD ascertainment	Objective/study question	Adjusting factors
Bahat (31)	April and June, 2020	A tertiary referral hospital, Turkey	Descriptive	44 SARS-CoV-2-positive (+) pregnant women who were hospitalized, >8 wk of gestation	Mean age: 28.57; female: 100%	Serum 25(OH)D <20 ng/mL	On the day of admission	To measure serum 25(OH)D concentration in SARS-CoV-2+ pregnant women	—
Baktash (47)	March 1 and April, 2020	General hospital in the UK	Prospective cohort	105 elderly (>65 y) participants, 70 SARS-CoV-2+, 35 SARS-CoV-2 negative (–)	Mean age: 81.28; patients: 60% male; healthy: 40%	Serum 25(OH)D ≤12 ng/mL	Concurrent with SARS-CoV-2 test	Relation between VDD and SARS-CoV-2 infection	No adjustment for confounders; another limitation is vitamin D intake after the acute phase of illness
Blanch-Rubió (37)	March 1 to May 3, 2020	Rheumatology service of hospital, Spain	Cross-sectional	2102 patients with noninflammatory rheumatic conditions	Mean age: 66.4; 80.5% female	—	—	Effect of vitamin D intake on COVID-19 incidence	Sex, age, comorbidities, treatment, and drugs
D'Avolio (48)	March 1 to April 14, 2020	Switzerland	Retrospective cohort	27 SARS-CoV-2+, 80 SARS-CoV-2–	Median age: 73; IQR (63 to 81); male: 54.2%	—	The vitamin D analysis was required to be conducted within 7 wk of the SARS-CoV-2 PCR result	Describing the 25(OH)D plasma concentrations in a cohort of patients from Switzerland	—
De Smet (42)	March 16 to April 16, 2020	General hospital in Belgium	Retrospective observational study	186 SARS-CoV-2+ hospitalized patients and 2717 diseased controls	Patients: median age, (IQR): 69 (52–80); male: 58.6%; controls: 68 (49–82); male: 36.8%	Serum 25(OH)D <20 ng/mL	Measured after SARS-CoV-2 test	Are lower 25(OH)D concentrations correlated with COVID-19?	—
Ferrari (43)	February to April, 2020	The San Raffaele Hospital, Milan, Italy	Retrospective cohort	128 SARS-CoV-2+, 219 SARS-CoV-2–	Patients: 64.8% males; male age: 62.7; female age: 69.3; healthy: 48.85% males; male age: 62.8, female age: 54.3	Serum 25(OH)D ≤30 ng/mL	The average time interval between SARS-CoV-2 test and their corresponding 25(OH)D measurements for the positive group was 33.9 and for the negative group was 33.33 d	—	—

There's many pages presenting characteristics of studies included in review – here are just a few of them

(Continued)

TABLE 1 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Definition of VitD deficiency	Time of VitD ascertainment	Objective/study question	Adjusting factors
Hernández (44)	March 10 to March 31, 2020	University Hospital, Spain	Retrospective case-control study	216 SARS-CoV-2+ and 197 population-based controls; in COVID-19 patients: number of VDD: 35; number of non-VDD: 162	Cases: age, median (IQR): 61.0 (47.5–70.0); controls: 61.0 (56.0–66.0); male: 62.4% in both groups	Serum 25(OH)D <20 ng/mL	At admission	To assess serum 25(OH)D concentrations in hospitalized patients with COVID-19 and to analyze the possible influence of vitamin D status on disease severity	—
Im (45)	February to June, 2020	Inha University Hospital, South Korea	Case-control	50 patients with SARS-CoV-2+ and 150 controls	Mean age: 57.5 in case and 52.2 in control groups; male: 58%	Serum 25(OH)D_3 <20 ng/mL	Within 7 d of admis?sion	Prevalence of VDD among COVID-19 patients, comparing vitamin D status between COVID-19 patients and healthy individuals	Control group was matched for age and sex with the COVID-19 group
Kerget (50)	March 24, to May 15, 2020	University Hospital in Turkey	Case-control	88 SARS-CoV-2+, 20 SARS-CoV-2−	Mean age: cases: 49.1; male: 60%; controls: 35.2; male: 40%	—	Fifth day of admission to hospital	To determine the relation of serum vitamin D concentration between patients and healthy controls	—
Luo (46)	February 27 to March 21, 2020	Hospital in China	Cross-sectional	335 COVID-19 patients, age- and sex-matched population of 560 individuals	Patients: median (IQR) age: 56 (43–64); male: 44.2%; controls: age: 55 (49.0–60.0); male: 45.9%	Serum 25(OH)D <30 ng/mL	In control, serum 25(OH)D concentrations were measured during the same period from 2018–2019; in patients, serum 25(OH)D concentrations were measured on admission	To investigate whether VDD is associated with COVID-19 incidence	Age, sex, comorbidities, smoking status, and BMI
Mardani (49)	March, 2020	A general clinic, Iran	Case-control	63 SARS-CoV-2+, 60 SARS-CoV-2−	Median age of 39; male: 52%	Deficient [25(OH)D <10 ng/mL], insufficient [25(OH)D: 10–30 ng/mL]	At baseline of the study	Relation between VDD and SARS-CoV-2 infection	Not adjusted

(*Continued*)

Varying definitions of deficiency
10-30ng/ml used in some papers

TABLE 2 Characteristics of studies investigated association of vitamin D status with COVID-19 severity[1]

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Abrishami (60)	February to April, 2020	Academic hospital in Iran	Retrospective study	73 SARS-CoV-2–positive (+) patients	Mean age: 55.18; male: 46.4%	To evaluate the prognostic role of serum 25(OH)D_3 on the extent of lung involvement and final outcome in patients with COVID-19	Lung involvement and mortality; serum 25(OH)D <25 ng/mL	At admission	For mortality, multivariate linear regression analysis adjusted for potential confounders including sex, age, and comorbidity
Anjum (62)	March to June, 2020	A hospital in Pakistan	Prospective	140 SARS-CoV-2+ patients	Mean age: 42.46; age range: 15–75; male: 58.57%	To determine the association between severe VDD and mortality in patients with COVID-19	Severity was defined as mortality; severe VDD was defined as 25(OH)D <10 ng/ml	At admission	—
Annweiler (56)	March to April, 2020	Nursing home in France	Quasi-experimental study with mean follow-up of 36 d	66 frail elderly nursing-home residents: intervention, *n* = 57; comparator, *n* = 9	Experiment: mean age: 87.7; male: 21% Comparator: mean age: 87.4; male: 33%	To evaluate COVID-19 severity and the use of COVID-19 drugs; the primary and secondary outcomes were COVID-19 mortality and OSCI score in acute phase	OSCI score	The intervention group received VitD3 (single dose of 80,000 IU every 2–3 mo) during COVID-19 or in the preceding month; the comparator group corresponded to all other participants	Age, gender, drugs, functional abilities, albuminuria
Annweiler (51)	March to May, 2020	One geriatric acute care unit dedicated to COVID-19 patients in France	Quasi-experimental study	Group 1 (*n* = 29), group 2 (*n* = 16), group 3 (*n* = 32)	Mean age: 88; male: 51%	14-day mortality and highest (worst) score on the OSCI measured during COVID-19 acute phase	To determine whether vitamin D3 supplementation taken either regularly over the preceding year or after the diagnosis of COVID-19 was	Group 1 (*n* = 29): supplemented regularly with VitD over the preceding year Group 2 (*n* = 16): supplemented with VitD after	Potential confounders were age, gender, functional abilities, undernutrition, chronic

Frail care home residents given Single dose 80,000 IU every 2-3mths

(*Continued*)

TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Pérez (66)	—	Hospital Central Military Mexico		172 patients with COVID-19; cases: those who died ($n = 35$); controls: those who survived	Mean age: 51.44; male: 77.3%	Determine the association between 25(OH)D concentrations and mortality in hospitalized patients with COVID-19	Mortality was considered as severe; 25(OH)D <20 ng/dL	—	—
Radujkovic (13)	March to June, 2020	Medical university hospital, Heidelberg, Germany	Cohort	185 patients; patients with VDD ($n = 41$); non-VDD ($n = 144$); outpatients: 92; inpatients: 93	Median age: 60, IQR (49–70); male: 51%	To explore possible associations of vitamin D status with disease severity and survival	Decision for inpatient vs. outpatient admission was based on spontaneous oxygen saturation, comorbidities, and the overall performance status; based on COVID-19 severity classifications, all inpatients had severe disease (defined as tachypnea, oxygen saturation <93% at rest, or ICU requirement); 25(OH)D <12 ng/mL	At the time of admission	Adjusted for age, gender, and comorbidities
Rastogi (14)	—	Tertiary care hospital in north India	RCT	40 Asymptomatic or mildly symptomatic SARS-CoV-2+ with VDD [$25(OH)D_3$ <20 ng/mL]	Median age in the intervention group: 50.0, IQR (36–51); male: 37.5% Control: 47.5 (39.3 to 49.2); male: 58.3%	Effect of high-dose oral cholecalciferol supplementation on SARS-CoV-2 viral clearance	—	At the beginning of study	—
Ye (41)	February to March, 2020	Guangxi People's Hospital, China	Case-control	80 healthy controls and 62 patients diagnosed with COVID-19	Median age in controls: 42, IQR (31–52); male: 40% Age in cases: 43(32–59); male: 37%	To examine the relation between serum $25(OH)D_3$ concentration and COVID-19 severity, and its clinical case characteristics	Severe COVID-19 case was defined according to the guidelines of the National Health Commission of China[5]; 25(OH)D <20 ng/dL	At admission	Demographics and comorbidities

(*Continued*)

RCT effect of high dose Vit D in VDD on viral clearance

Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, PuriGD,Malhotra P. Short term, high-dose vitamin supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). Postgrad Med J 2020;1–4.

Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study)

Ashu Rastogi,[1] Anil Bhansali,[1] Niranjan Khare,[2] Vikas Suri,[2] Narayana Yaddanapudi,[3] Naresh Sachdeva,[1] G D Puri,[3] Pankaj Malhotra [2]

► Supplemental material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/postgradmedj-2020-139065).

[1]Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[2]Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[3]Anaesthesia, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to
Pankaj Malhotra, Department Of Internal Medicine, Nehru Hospital, PGIMER, Chandigarh 160012, India; malhotrapankaj@hotmail.com

All the authors had access to the data and were involved in writing the manuscript as per ICMJE criteria.

Received 19 September 2020
Revised 19 October 2020
Accepted 29 October 2020

To cite: Rastogi A, Bhansali A, Khare N, *et al. Postgrad Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/postgradmedj-2020-139065

ABSTRACT

Background Vitamin D has an immunomodulatory role but the effect of therapeutic vitamin D supplementation in SARS-CoV-2 infection is not known.

Aim Effect of high dose, oral cholecalciferol supplementation on SARS-CoV-2 viral clearance.

Design Randomised, placebo-controlled.

Participants Asymptomatic or mildly symptomatic SARS-CoV-2 RNA positive vitamin D deficient (25(OH) D<20 ng/ml) individuals.

Intervention Participants were randomised to receive daily 60 000 IU of cholecalciferol (oral nano-liquid droplets) for 7 days with therapeutic target 25(OH) D>50 ng/ml (intervention group) or placebo (control group). Patients requiring invasive ventilation or with significant comorbidities were excluded. 25(OH)D levels were assessed at day 7, and cholecalciferol supplementation was continued for those with 25(OH)D <50 ng/ml in the intervention arm. SARS-CoV-2 RNA and inflammatory markers fibrinogen, D-dimer, procalcitonin and (CRP), ferritin were measured periodically.

Outcome measure Proportion of patients with SARS-CoV-2 RNA negative before day-21 and change in inflammatory markers.

Results Forty SARS-CoV-2 RNA positive individuals were randomised to intervention (n=16) or control (n=24) group. Baseline serum 25(OH)D was 8.6 (7.1 to 13.1) and 9.54 (8.1 to 12.5) ng/ml (p=0.730), in the intervention and control group, respectively. 10 out of 16 patients could achieve 25(OH)D>50 ng/ml by day-7 and another two by day-14 [day-14 25(OH)D levels 51.7 (48.9 to 59.5) ng/ml and 15.2 (12.7 to 19.5) ng/ml (p<0.001) in intervention and control group, respectively]. 10 (62.5%) participants in the intervention group and 5 (20.8%) participants in the control arm (p<0.018) became SARS-CoV-2 RNA negative. Fibrinogen levels significantly decreased with cholecalciferol supplementation (intergroup difference 0.70 ng/ml; P=0.007) unlike other inflammatory biomarkers.

Conclusion Greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in fibrinogen on high-dose cholecalciferol supplementation.

Trial register number NCT04459247.

INTRODUCTION

Coronavirus-2019 (COVID-19) caused by severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) has affected the lives of millions of individuals globally and severely strained the medical community. Pre-symptomatic and asymptomatic SARS-CoV-2 positive individuals far outnumber the symptomatic ones or those with severe disease.[1 2] The transmission potential of SARS CoV-2 is potentially greater than earlier viral outbreaks of SARS-CoV and MERS-CoV because of its high transmissibility even from asymptomatic SARS-CoV-2 RNA positive individuals.[3] Routine measures of social distancing, personal hand hygiene and limited outdoor contact activities have shown benefits to limit corona virus infection. But identification of asymptomatic carriers of SARS-CoV-2 infection is paramount to contain viral infection.[2] Anti-viral, anti-inflammatory drugs and convalescent plasma therapy have been used for COVID-19 with variable results.[4]

It has been observed that vitamin D-deficient individuals have increased COVID-19 risk and mortality.[5–7] The role of vitamin D in SARS-CoV-2 infection is not explored in intervention studies despite the knowledge of an immunomodulatory role and protective effect of vitamin D against other viral infections.[8] An intervention study with calcifediol noticed a reduction in requirement for intensive care among hospitalised patients for COVID19.[9] However, vitamin D levels were neither available at baseline nor during follow up in the study. It is noticed that those receiving vitamin D supplementation have fewer respiratory tract infections.[8] However, the immune-modulatory effect of vitamin D is likely to be observed at 25(OH)D levels, which are considered higher than that required for its skeletal effects.[10–12]

The role of therapeutic vitamin D supplementation in asymptomatic individuals with vitamin-D deficiency and SARS-CoV-2 infection is not known. A PCR-confirmed SARS-COV-2 infection from nasopharyngeal swab pertains to relevant clinical outcome in intervention trials[10] especially for asymptomatic individuals as an earlier SARS-CoV-2 negativity would have significant public health benefits in limiting the spread of the disease. Therefore, we hypothesise that high-dose cholecalciferol supplementation in patients with SARS-CoV-2 infection and vitamin D deficiency may lead to SARS-CoV-2 negativity in greater proportions of patients with a decrease in serological markers of inflammation.

“ **Intervention**

Participants were randomised to receive daily 60 000 IU of cholecalciferol (oral nano-liquid droplets) for 7 days with therapeutic target 25(OH)D>50 ng/ml (intervention group) or placebo (control group). Patients requiring invasive ventilation or with significant comorbidities were excluded. 25(OH)D levels were assessed at day 7, and cholecalciferol supplementation was continued for those with 25(OH)D <50 ng/ml in the intervention arm. SARS-CoV-2 RNA and inflammatory markers fibrinogen, D-dimer, procalcitonin and (CRP), ferritin were measured periodically.

Outcome measure Proportion of patients with SARS-CoV-2 RNA negative before day-21 and change in inflammatory markers with a significant decrease in fibrinogen on high-dose cholecalciferol supplementation.”

from previous paper

"**Results** Forty SARS-CoV-2 RNA positive individuals were randomised to intervention (n=16) or control (n=24) group. Baseline serum 25(OH)D was 8.6 (7.1 to 13.1) and 9.54 (8.1 to 12.5) ng/ml (p=0.730), in the intervention and control group, respectively. 10 out of 16 patients could achieve 25(OH)D>50 ng/ml by day-7 and another two by day-14 [day-14 25(OH)D levels 51.7 (48.9 to 59.5) ng/ml and 15.2 (12.7 to 19.5) ng/ml (p<0.001) in intervention and control group, respectively]. 10 (62.5%) participants in the intervention group and 5 (20.8%) participants in the control arm (p<0.018) became SARS-CoV-2 RNA negative. Fibrinogen levels significantly decreased with cholecalciferol supplementation (intergroup difference 0.70 ng/ml; P=0.007) unlike other inflammatory biomarkers. **Conclusion** Greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in fibrinogen on high-dose cholecalciferol supplementation."

Makes argument for Vit D suppleme-ntation, saying risks are small

Worth a read in full

Rapid Response:

Vitamin D Mitigates COVID-19, Say 40+ Patient Studies (listed below) – Yet BAME, Elderly, Care-homers, and Obese are still 'D' deficient, thus at greater COVID-19 risk - WHY?

Dear Editor

Vitamin D reduces COVID-19; infection; severity; ICU admission and mortality: as clearly evidenced by; immune biology, observational and interventional studies, and wider considerations of; latitude, seasonal UVB exposure, and national supplementation policies: the uncertainty is the quantum: but studies suggest 'D' effects are likely large - 50% less infectivity – multiples lower ICU and mortality rate.

Vitamin D is a steroid hormone, also present in limited dietary sources. For most, the major 'D' source is skin exposure to UVB in sunlight, which waxes and wanes seasonally. Supplementation is the only other option. 'D' with 50 metabolites[1] is more bio-actively influential than appreciated. Sensible 'D' supplementation has a 100-year track-record.[2] Side-effects are minimal.

Dexamethasone in the same structural steroid family as 'D', shares common VDR (vitamin-D-receptor)[3] and related gene pathways,[4] is artificial, and in some circumstances mitigates against COVID-19, albeit with variable side-effects. Dexamethasone is clearly a useful adjunct.

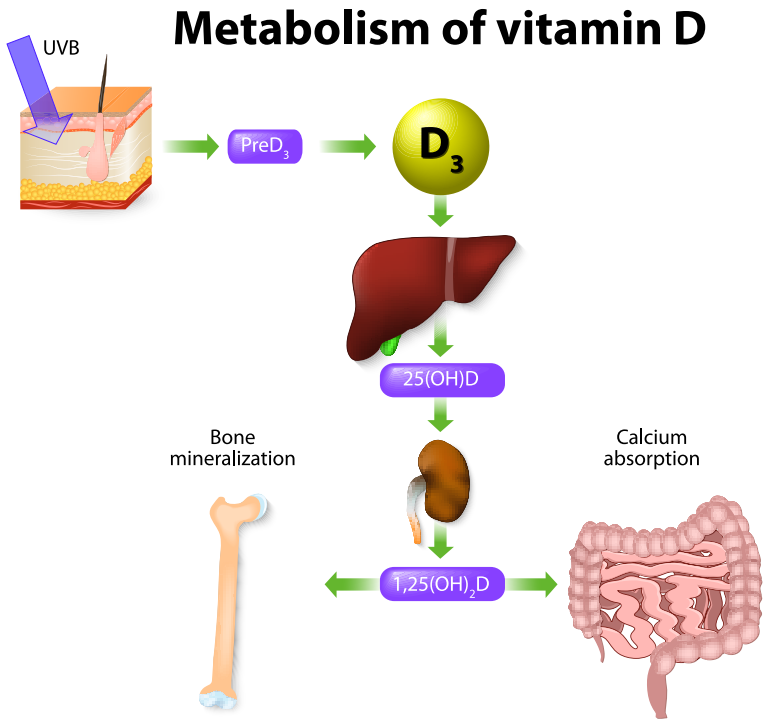
'D' deficiencies are widespread globally,[5] and particularly in; BAME, African Americans, Elderly, Carehomers,[6, 7] (Reality-check ref.) and Obese Persons; groups also at high-risk of COVID-19. Regions with proactive Vitamin-D-policies, education, nutritional supplementation, and/or greater UVB exposure, have much lower COVID-19 infection and mortality; e.g. Finland, Norway, New Zealand and, Equatorial-Africa (despite poverty / high urban-multi-person-dwelling-occupation).

Appropriate vitamin D supplementation risks are small: rewards huge. Public policy application of Bradford-Hill risk / harm criteria, used for smoking, social-distancing and masks, would support[8] 'D' supplementation of at-risk groups, and 'D' testing of all COVID-19 hospital patients.

BMJ 2020;371:m3872

https://www.bmj.com/content/371/bmj.m3872/rr-5

Pre-covid NNDS data suggest 29% of UK adults deficient in Vitamin D



British Nutrition Foundation (2019) NDNS: Time Trend and Income Analyses forYears 1 to 9. Available at: https://bit.ly/2yEIFbe (accessed 18.03.2020)

Vitamin D deficiency is relatively common in the UK as the recent National Diet and Nutrition Survey (NDNS) analysis of the last 9 years reported that from January to March 19% of children aged 4 to 10 years, **37% of children aged 11 to 18 years and 29% of adults had low Vitamin D levels (25-OHD below 25nmol/L**) which is defined as the threshold indicating risk of deficiency.

Image: Sourced from Shutterstock

2020 BMJ Vitamin D and COVID-19 article

"The overarching messages are as follows:

(1)Vitamin D is essential for good health.

(2) Many people, particularly those living in northern latitudes (such as the UK, Ireland, Northern Europe, Canada and the northern parts of the USA, northern India and China), have poor vitamin D status, especially in winter or if confined indoors. (3)

BMJ Nutrition, Prevention & Health

Vitamin D and SARS-CoV-2 virus/ COVID-19 disease

Susan A Lanham-New,[1] Ann R Webb,[2] Kevin D Cashman,[3] Judy L Buttriss,[4] Joanne L Fallowfield,[5] Tash Masud,[6] Martin Hewison,[7] John C Mathers,[8] Mairead Kiely,[3] Ailsa A Welch,[9] Kate A Ward,[10] Pamela Magee,[11] Andrea L Darling,[1] Tom R Hill,[8] Carolyn Greig,[12] Colin P Smith,[13] Richard Murphy,[14] Sarah Leyland,[15] Roger Bouillon,[16] Sumantra Ray,[11,17,18] Martin Kohlmeier [18,19]

To cite: Lanham-New SA, Webb AR, Cashman KD, *et al*. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. *BMJ Nutrition, Prevention & Health* 2020;**0**. doi:10.1136/bmjnph-2020-000089

For numbered affiliations see end of article.

Correspondence to
Professor Susan A Lanham-New, Nutritional Sciences, University of Surrey Faculty of Health and Medical Sciences, Guildford GU2 7XH, UK;
s.lanham-new@surrey.ac.uk

Received 16 April 2020
Revised 29 April 2020
Accepted 30 April 2020

BACKGROUND AND AIM

The spread of novel SARS-CoV-2 virus, and the disease COVID-19 that is caused by SARS-CoV-2, continues apace. Saving lives and slowing the worldwide pandemic remain of utmost importance to everyone: the public, healthcare professionals, scientists, industry and governments.

It is absolutely essential that advice given to the public is evidence-based, accurate and timely; anything less would mislead and has the potential to cause harm. Popular information channels, such as social media platforms, have been rife with misinformation that has been perpetuated by fear and uncertainty. This has been the case particularly for diet and lifestyle advice. There are recommendations for the prevention of the spread of COVID-19 from the WHO,[1] the UK,[2] Irish[3] and USA[4] governments and the European Commission,[5] as well as public health and healthcare agencies, including key direction on self-isolation.[6]

This short original report aims to provide a balanced scientific view on vitamin D and SARS-CoV-2 virus/COVID-19 disease. It provides a succinct summary of the current scientific evidence of associations between vitamin D, influenza, upper respiratory tract infections (URTIs) and immune health. Importantly, the paper concludes with lifestyle strategies for avoiding vitamin D deficiency and ensuring a healthy balanced diet at any time, including during the current pandemic. The overarching messages are as follows: (1) Vitamin D is essential for good health. (2) Many people, particularly those living in northern latitudes (such as the UK, Ireland, Northern Europe, Canada and the northern parts of the USA, northern India and China), have poor vitamin D status, especially in winter or if confined indoors. (3) Low vitamin D status may be exacerbated during this COVID-19 crisis (eg, due to indoor living and hence reduced sun exposure), and anyone who is self-isolating with limited access to sunlight is advised to take a vitamin D supplement according to their government's recommendations for the general population (ie, 400 IU/day for the UK[7] and 600 IU/day for the USA (800 IU for >70 years))[8] and the European Union (EU).[9] (4) There is no strong scientific evidence to show that very high intakes (ie, mega supplements) of vitamin D will be beneficial in preventing or treating COVID-19. (5) There are evidenced health risks with excessive vitamin D intakes especially for those with other health issues such as a reduced kidney function.

NUTRITION, VITAMIN D AND IMMUNITY

Good nutrition and lifestyle factors (such as physical activity) have a positive impact on immune function, promoting biological and physiological systems and processes that enable humans to resist infection. In light of the current COVID-19 pandemic, and given the importance of diet to overall health and well-being, nutrients (macro and micro) deserve special attention.[10] As a key micronutrient, vitamin D should be given particular focus—not as a 'magic bullet' to beat COVID-19, as the scientific evidence base is severely lacking at this time—but rather as part of a healthy lifestyle strategy to ensure that populations are nutritionally in the best possible place.[11]

Vitamin D is unique: it is a prohormone which is produced in the skin during exposure to sunlight (UVB radiation at 290–315 nm) with, usually, smaller amounts obtained from food. During the winter months in areas of middle-high latitude, the solar elevation

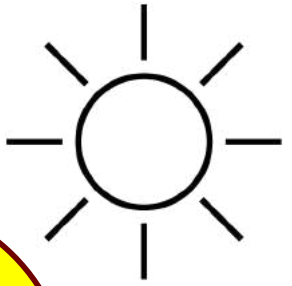
Cont'd….

Low vitamin D status may be exacerbated during this COVID-19 crisis (e.g., due to indoor living and hence reduced sun exposure), and anyone who is self-isolating with limited access to sunlight is advised to take a vitamin D supplement according to their government's recommendations for the general population (ie, 400 IU/day for the UK[7] and 600 IU/day for the USA (800 IU for >70 years))[8] and the European Union (EU).[9] (4)

There is no strong scientific evidence to show that very high intakes (ie, mega supplements) of vitamin D will be beneficial in preventing or treating COVID-19.

(5) There are evidenced health risks with excessive vitamin D intakes especially for those with other health issues such as a reduced kidney function".

Vitamin D



Vitamin D deficiency is common in people who are housebound or institutionalised.

Skin pigmentation also affects levels of production and skin with more pigmentation will produce less, so deficiency is more common in people with darker skin (Richard et al., 2017).

Both obesity and diabetes are also associated with high rates of Vitamin D deficiency (Via, 2012).

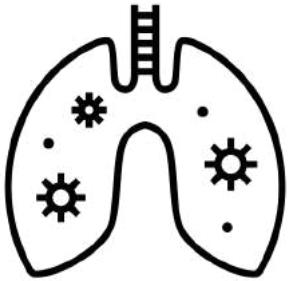
Recap: Vitamin D Food sources

Foods containing vitamin D include oily fish, fortified cereals, eggs and mushrooms that have been exposed to sunlight.

Richard, A., Rohrmann, S., & Quack Lötscher, K. C. (2017). Prevalence of Vitamin D Deficiency and Its Associations with Skin Color in Pregnant Women in the First Trimester in a Sample from Switzerland. Nutrients, 9(3), 260. https://doi.org/10.3390/nu9030260

Via M. (2012) The Malnutrition of Obesity: Micronutrient Deficiencies That Promote Diabetes International Scholarly Research Network *ISRN Endocrinology* Volume 2012, Article ID 103472

Mechanisms: Vitamin D and COVID-19



nutrients

MDPI

Review

Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

William B. Grant [1,*], Henry Lahore [2], Sharon L. McDonnell [3], Carole A. Baggerly [3], Christine B. French [3], Jennifer L. Aliano [3] and Harjit P. Bhattoa [4]

[1] Sunlight, Nutrition, and Health Research Center, P.O. Box 641603, San Francisco, CA 94164-1603, USA
[2] 2289 Highland Loop, Port Townsend, WA 98368, USA; hlahore@vitamindwiki.com.
[3] GrassrootsHealth, Encinitas, CA 92024, USA; Sharon@grassrootshealth.org (S.L.M.); carole@grassrootshealth.org (C.A.B.); Christine@grassrootshealth.org (C.B.F.); jen@grassrootshealth.org (J.L.A.)
[4] Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Nagyerdei Blvd 98, H-4032 Debrecen, Hungary; harjit@med.unideb.hu
* Correspondence: wbgrant@infionline.net; Tel.: +1-415-409-1980

Received: 12 March 2020; Accepted: 31 March 2020; Published: 2 April 2020

check for updates

Abstract: The world is in the grip of the COVID-19 pandemic. Public health measures that can reduce the risk of infection and death in addition to quarantines are desperately needed. This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D_3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D_3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.

Keywords: acute respiratory distress syndrome (ARDS); ascorbic acid; cathelicidin; coronavirus; COVID-19; cytokine storm; influenza; observational; pneumonia; prevention; respiratory tract infection; solar radiation; treatment; UVB; vitamin C; vitamin D

1. Introduction

The world is now experiencing its third major epidemic of coronavirus (CoV) infections. A new CoV infection epidemic began in Wuhan, Hubei, China, in late 2019, originally called 2019-nCoV [1]

"Vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines.

Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not".

Mechanisms

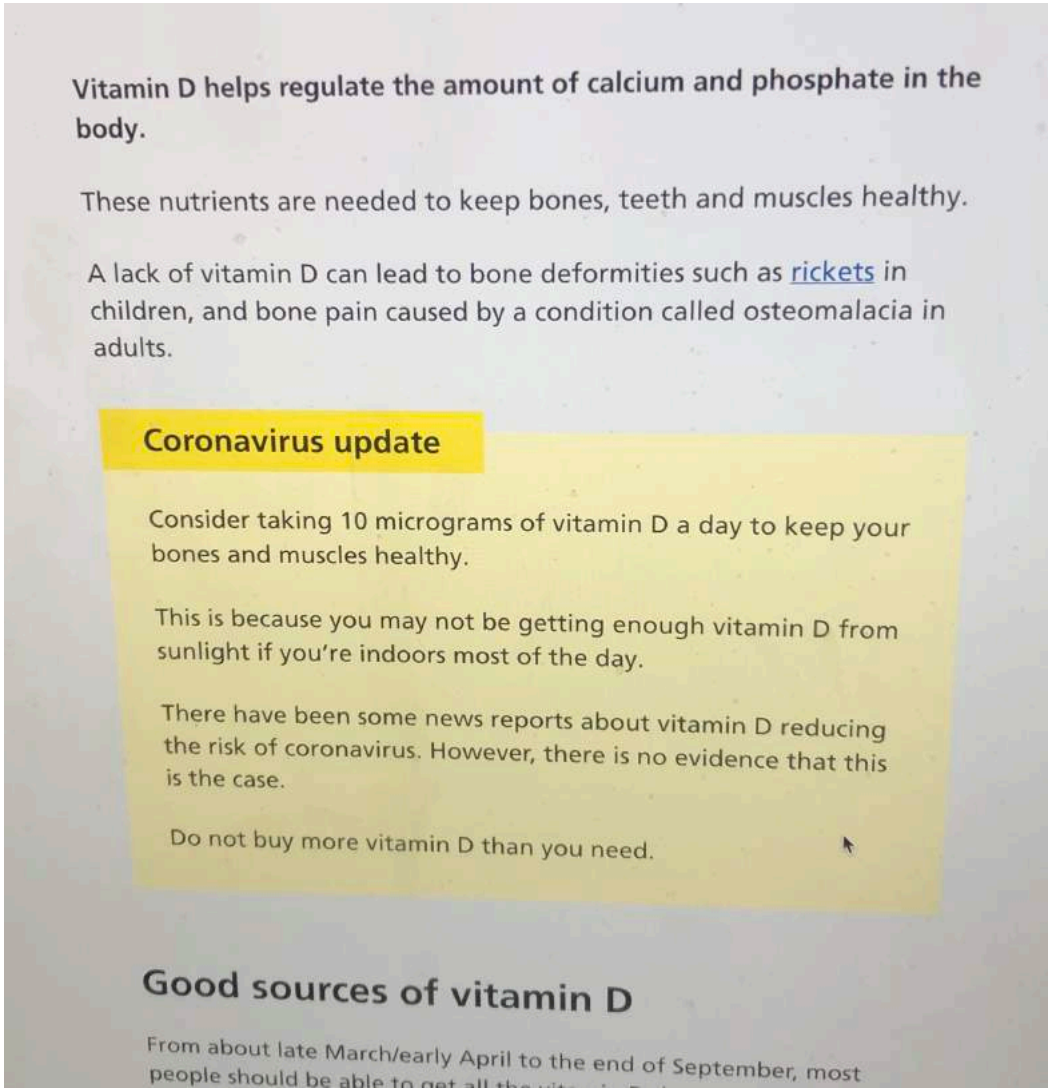
More from previous paper

“

“vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations”.

NHS Covid advice and Vitamin D

- https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/



Vitamin D helps regulate the amount of calcium and phosphate in the body.

These nutrients are needed to keep bones, teeth and muscles healthy.

A lack of vitamin D can lead to bone deformities such as rickets in children, and bone pain caused by a condition called osteomalacia in adults.

Coronavirus update

Consider taking 10 micrograms of vitamin D a day to keep your bones and muscles healthy.

This is because you may not be getting enough vitamin D from sunlight if you're indoors most of the day.

There have been some news reports about vitamin D reducing the risk of coronavirus. However, there is no evidence that this is the case.

Do not buy more vitamin D than you need.

Good sources of vitamin D

From about late March/early April to the end of September, most people should be able to get all the

Recap: UK guidelines on Vitamin D requirements

- Dietary reference value (DRV) – 10 µg/day (400IU) for all age 4 years or over, including pregnant & lactating women
- Safe intake of 8.5-10 µg/day for infants up to 11months
- Safe intake of 10µg/day for age 12 months – 4 years

https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report

What is Long Covid?

Long Covid Syndrome?

Controversial, knowledge STILL emerging…

COVID-19 beyond the acute phase of infection is being investigated…

Reports suggesting residual effects of SARS-CoV-2 infection include fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia and decline in quality of life, malnutrition and muscle weakness.

Mast cell activation?

Therapy

Personalised – carers?

Testing - via GP?

Client preferences & goals

Address underpinning imbalances, triggers/mediators

e.g. metabolic dysfunction

?

Nutrition therapy

Foundations?

Food first in general – but sometimes use supplements first if think it will help may person feel better and better able to make changes, nutrient dense balanced diet as foundation

Economic / low waste, think about financial circumstances of individual and family, physical ability to shop, cook, eat, chew…

Convenient / easy to prepare – maybe fatigued

Useful 2021 article re supplements

" The potential anti-coronavirus benefits of micronutrients and macronutrients (ie, minerals, vitamins, lipids, proteins and polyphenols) to combat COVID-19 infection through inhibition of viral targets on human cell surface (i.e., angiotensin-converting enzyme"

NT Food and Nutrition

Coronavirus and Nutrition

What Is the Evidence for Dietary Supplements Usage for COVID-19 Control and Management?

A. Satyanarayan Naidu, PhD
Peter Pressman, MD, PhD
Roger A. Clemens, DrPH

In the wake of the COVID-19 pandemic, global medical research has undertaken a relentless quest to unravel the virulence mechanisms of SARS-CoV-2, the innate barriers of host defense, the surveillance of progress toward herd immunity, and the attempts to quickly identify and evaluate novel or alternative coronavirus interventions. This nutrition update highlights the important role of dietary factors in achieving optimum health and also explores possible approaches to augmenting innate host defenses. The potential anti-coronavirus benefits of micronutrients and macronutrients (ie, minerals, vitamins, lipids, proteins and polyphenols) to combat COVID-19 infection through inhibition of viral targets on human cell surface (ie, angiotensin-converting enzyme 2) for docking, entry, and replication and, furthermore, to regulate immune and inflammatory responses (cytokine storm), oxidative stress (redox imbalance), and normal signaling pathways to the reduce health risks among vulnerable populations (ie, elderly) with metabolic disorders (ie, obesity, diabetes, cardiovascular disease, hypertension, asthma) and recovery of patients to normal health are discussed. Nutr Today. 2021;00(1):00–00

Since the first outbreak of coronavirus disease 2019 (COVID-19) in November 2019 in Wuhan, China, more than 122 000 peer-reviewed scientific articles have been published about this viral pandemic. Approximately 5500 clinical trials have been initiated, and numerous pharmacological agents and an array of antivirals, corticosteroids, or their combinations have been administered to patients worldwide. However, to date, no specific or definitively efficacious antiviral intervention is available for COVID-19. Therefore, a multidimensional strategy is at this time the most desirable to achieve successful global health outcomes.

According to a recent report, consumer interests in dietary supplements for immune support and overall health have skyrocketed during the COVID-19 pandemic. Diet and nutrition are fundamental for an effective host defense, whereas malnutrition could seriously compromise immune competence. Global experience with COVID-19 outbreaks emphasizes the significance of rapid diagnosis of malnutrition and immediate implementation of calorie/protein-balanced nutrition care. These protocols are recommended by several health agencies to achieve therapeutic success in lowering mortality rates in severe COVID-19 cases.[1]

This review updates the impact of nutritional status on the overall host defense and virulence of COVID-19. Considering the epidemiological differences in coronavirus (CoV) transmission and varied symptomatic outcomes of infected individuals, we arrange the nutritional interventions into 3 categories: (i) immune nutrition, (ii) redox nutrition, and (iii) nutrient-related disruption of viral entry and replication. A few bioactives, naturally present in food, for which there is some (although not yet conclusive) evidence of possible activity in each category, are discussed. Figure presents these categories.

It is important to note that the anti-CoV effects of several micronutrients and bioactive compounds are still preliminary. Randomized clinical trials (RCTs) are needed to unravel their safety, efficacy, and modes of action. Pharmacokinetic data should establish the ADME (absorption, distribution, metabolism, and excretion) profiles of these compounds. Furthermore, the bioavailability, dosage, tolerance, and drug interactions (if any) of these nutrients should be established. Once efficacy data are available, it is possible that after regulatory evaluation of a bioactive compound or "nutraceutical," a product may qualify as potential prophylactic or adjuvant therapy (likely a drug classification in the United States) for the control and

A Satyanarayan Naidu, PhD, is the Director of N-terminus Research Laboratory in Yorba Linda, California and a fellow of the Royal Society for Medicine and the Linnean Society of London, Nterminus.

Peter Pressman, MD, PhD, is Vice President of Medical Operations at Polyscience Consulting, Los Angeles, California, and a Fellow of the American College of Nutrition.

Roger A. Clemens, DrPH, is an expert in nutrition, food safety and toxicology, and food processing. He is an adjunct professor of pharmacology and pharmaceutical sciences as well as quality and regulatory science at the University of Southern California School of Pharmacy. He is former president of the Institute of Food Technologists and was a member of the Dietary Guidelines Advisory Committee in 2010.

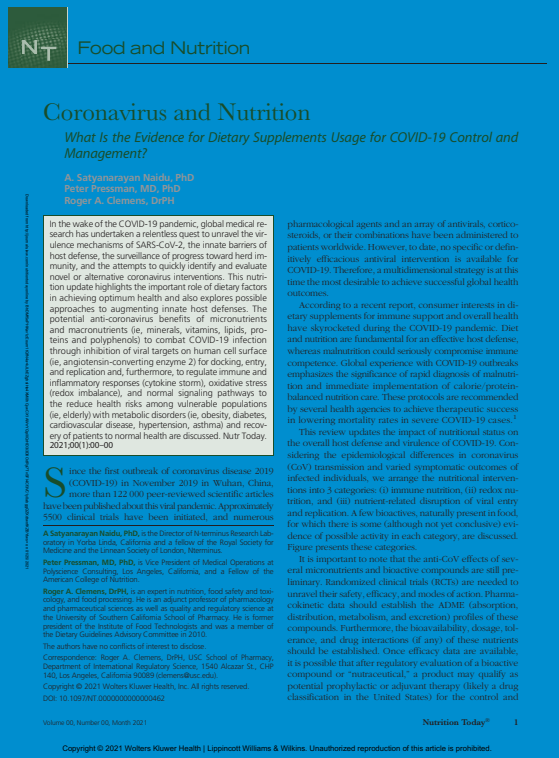
The authors have no conflicts of interest to disclose.

Correspondence: Roger A. Clemens, DrPH, USC School of Pharmacy, Department of International Regulatory Science, 1540 Alcazar St., CHP 140, Los Angeles, California 90089 (clemens@usc.edu).

DOI: 10.1097/NT.0000000000000462

Useful 2021 article re supplements

"for docking, entry, and replication and, furthermore, to regulate immune and inflammatory responses (cytokine storm), oxidative stress (redox imbalance), and normal signaling pathways to the reduce health risks among vulnerable populations (i. e, elderly) with metabolic disorders (i. e, obesity, diabetes, cardiovascular disease, hypertension, asthma) and recovery of patients to normal health are discussed "



NT Food and Nutrition

Coronavirus and Nutrition

What Is the Evidence for Dietary Supplements Usage for COVID-19 Control and Management?

A. Satyanarayan Naidu, PhD
Peter Pressman, MD, PhD
Roger A. Clemens, DrPH

In the wake of the COVID-19 pandemic, global medical research has undertaken a relentless quest to unravel the virulence mechanisms of SARS-CoV-2, the innate barriers of host defense, the surveillance of progress toward herd immunity, and the attempts to quickly identify and evaluate novel or alternative coronavirus interventions. This nutrition update highlights the important role of dietary factors in achieving optimum health and also explores possible approaches to augmenting innate host defenses. The potential anti-coronavirus benefits of micronutrients and macronutrients (ie, minerals, vitamins, lipids, proteins and polyphenols) to combat COVID-19 infection through inhibition of viral targets on human cell surface (ie, angiotensin-converting enzyme 2) for docking, entry, and replication and, furthermore, to regulate immune and inflammatory responses (cytokine storm), oxidative stress (redox imbalance), and normal signaling pathways to the reduce health risks among vulnerable populations (ie, elderly) with metabolic disorders (ie, obesity, diabetes, cardiovascular disease, hypertension, asthma) and recovery of patients to normal health are discussed. Nutr Today. 2021;00(1):00–00

Since the first outbreak of coronavirus disease 2019 (COVID-19) in November 2019 in Wuhan, China, more than 122 000 peer-reviewed scientific articles have been published about this viral pandemic. Approximately 5500 clinical trials have been initiated, and numerous pharmacological agents and an array of antivirals, corticosteroids, or their combinations have been administered to patients worldwide. However, to date, no specific or definitively efficacious antiviral intervention is available for COVID-19. Therefore, a multidimensional strategy is at this time the most desirable to achieve successful global health outcomes.

According to a recent report, consumer interests in dietary supplements for immune support and overall health have skyrocketed during the COVID-19 pandemic. Diet and nutrition are fundamental for an effective host defense, whereas malnutrition could seriously compromise immune competence. Global experience with COVID-19 outbreaks emphasizes the significance of rapid diagnosis of malnutrition and immediate implementation of calorie/protein-balanced nutrition care. These protocols are recommended by several health agencies to achieve therapeutic success in lowering mortality rates in severe COVID-19 cases.[1]

This review updates the impact of nutritional status on the overall host defense and virulence of COVID-19. Considering the epidemiological differences in coronavirus (CoV) transmission and varied symptomatic outcomes of infected individuals, we arrange the nutritional interventions into 3 categories: (i) immune nutrition, (ii) redox nutrition, and (iii) nutrient-related disruption of viral entry and replication. A few bioactives, naturally present in food, for which there is some (although not yet conclusive) evidence of possible activity in each category, are discussed. Figure presents these categories.

It is important to note that the anti-CoV effects of several micronutrients and bioactive compounds are still preliminary. Randomized clinical trials (RCTs) are needed to unravel their safety, efficacy, and modes of action. Pharmacokinetic data should establish the ADME (absorption, distribution, metabolism, and excretion) profiles of these compounds. Furthermore, the bioavailability, dosage, tolerance, and drug interactions (if any) of these nutrients should be established. Once efficacy data are available, it is possible that after regulatory evaluation of a bioactive compound or "nutraceutical," a product may qualify as potential prophylactic or adjuvant therapy (likely a drug classification in the United States) for the control and

A Satyanarayan Naidu, PhD, is the Director of N-terminus Research Laboratory in Yorba Linda, California and a Fellow of the Royal Society for Medicine and the Linnean Society of London, Nterminus.

Peter Pressman, MD, PhD, is Vice President of Medical Operations at Polyscience Consulting, Los Angeles, California, and a Fellow of the American College of Nutrition.

Roger A. Clemens, DrPH, is an expert in nutrition, food safety and toxicology, and food processing. He is an adjunct professor of pharmacology and pharmaceutical sciences as well as quality and regulatory science at the University of Southern California School of Pharmacy. He is former president of the Institute of Food Technologists and was a member of the Dietary Guidelines Advisory Committee in 2010.

The authors have no conflicts of interest to disclose.

Correspondence: Roger A. Clemens, DrPH, USC School of Pharmacy, Department of International Regulatory Science, 1540 Alcazar St., CHP 140, Los Angeles, California 90089 (clemens@usc.edu).

DOI: 10.1097/NT.0000000000000462

Paper identifies 3 roles for supplements

- Immune nutrition: Zn, Vit C, β glucans, curcumin, flavonoids, polyphenols
- Redox nutrition: Se, astaxanthin, lactoferrin
- Nutrient-related disruption of viral entry and replication: Vit D, Resveratrol, quercetin

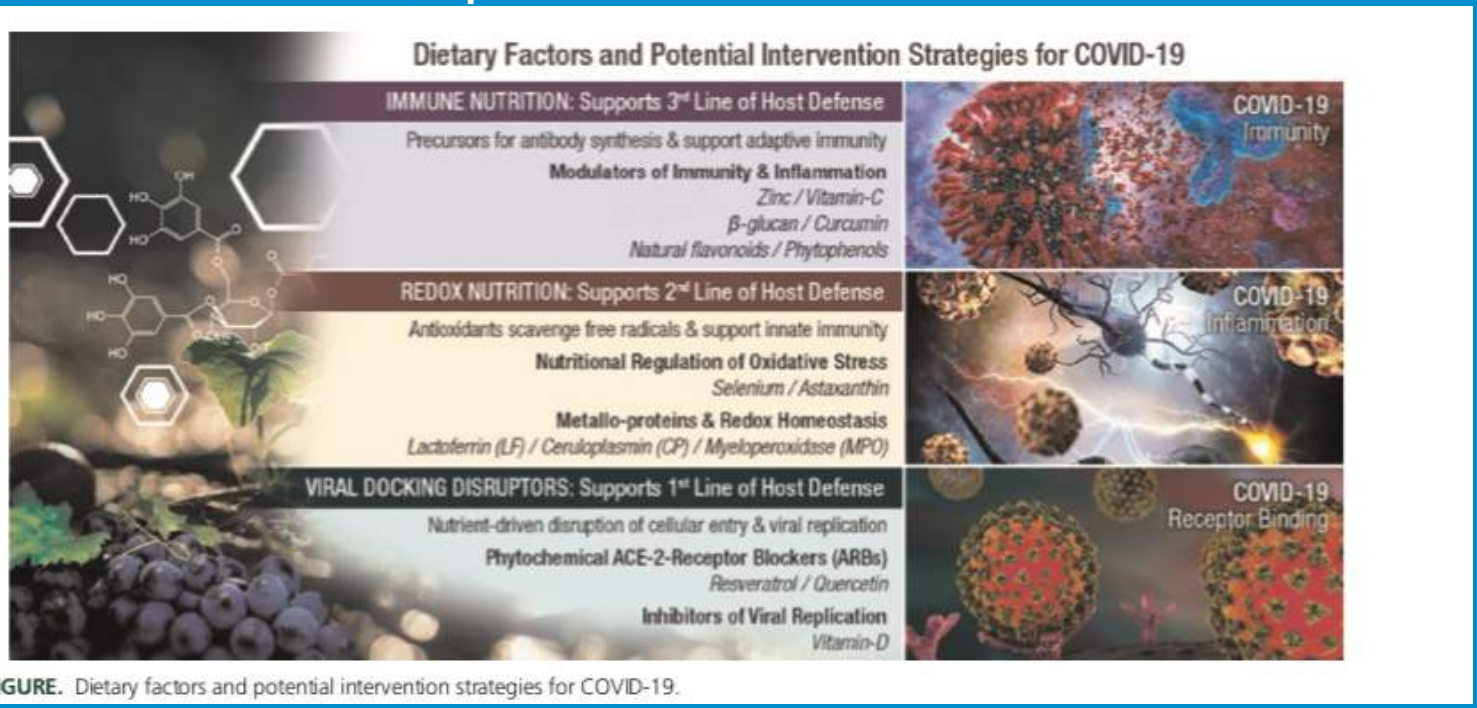


FIGURE. Dietary factors and potential intervention strategies for COVID-19.

BUT Paper states evidence is preliminary….

"It is important to note that the anti-CoV effects of several micronutrients and bioactive compounds are still preliminary. Randomized clinical trials (RCTs) are needed to unravel their safety, efficacy, and modes of action. Pharmacokinetic data should establish the ADME (absorption, distribution, metabolism, and excretion) profiles of these compounds. Furthermore, the bioavailability, dosage, tolerance, and drug interactions (if any) of these nutrients should be established. Once efficacy data are available, it is possible that after regulatory evaluation of a bioactive compound or "nutraceutical," a product may qualify as potential prophylactic or adjuvant therapy (likely a drug classification in the United States) "

Thank you for listening

- Will join panel Q & A
- Worcester virtual stand at BANT conference, look out for UoW poster presentations including one by Miranda Harris and Alison Benbow on NT clinical outcomes

- j.bold@worc.ac.uk boldj@cardiff.ac.uk

twitter *@justineboldfood*

justine_bold

Nutrition Health Worcester