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community resilience. The Hawaii State Commission on the Status of Women,⁵ for example, has proposed a post-pandemic recovery plan that advocates adopting universal basic income and single-payer health care, improving maternal and neonatal health care, addressing gender-based violence, and supporting Native, Black, and immigrant women. The Commission argues: "Rather than rush to rebuild the status quo of inequality, we should encourage a deep structural transition to an economy that better values the work we know is essential to sustaining us. We should also address the crises in health care, social, ecological, and economic policies laid bare by the epidemic."

Drawing on literature regarding the developmental origins of health and disease, we argue that recovery plans should also pay attention to groups who are not showing high COVID-19 morbidity and mortality rates now, but whose experiences and exposures substantially affect community health in the long term, especially mothers and children. Disinvesting in maternal and child health during the period of economic recession following the pandemic will sow the seeds of later health inequality and NCD risk, which will undermine community resilience to future health emergencies.

Although the rallying cry that "we're all in this together" might encourage members of society to help reduce the spread of the virus, it also hides the fact that some groups are affected much more than others. We argue for community-led and state-supported initiatives for building resilience that focus on the most vulnerable among us, and allow individuals, families, and communities to support each other in times of crisis and beyond. Any ethical new normal must encompass substantial systemic change that focuses on social, reproductive, and health justice and redefines the socioeconomic conditions we consider acceptable.

We declare no competing interests.

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- 1 Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020; **8**: e21.
- 2 Spanakis EK, Golden SH. Race/ethnic difference in diabetes and diabetic complications. *Curr Diab Rep* 2013; **13**: 814–23.
- 3 Penkler M, Hanson M, Biesma R, Müller R. DOHaD in science and society: emergent opportunities and novel responsibilities. *J Dev Orig Health Dis* 2019; **10**: 268–73.
- 4 Krieger N. Embodiment: a conceptual glossary for epidemiology. *J Epidemiol Community Health* 2005; **59**: 350–55.
- 5 Hawai'i State Commission on the Status of Women. Building bridges, not walking on backs: a feminist economic recovery plan for COVID-19. April 14, 2020. <https://humanservices.hawaii.gov/wp-content/uploads/2020/04/4.13.20-Final-Cover-D2-Feminist-Economic-Recovery-D1.pdf> (accessed June 16, 2020).

Metabolic health and COVID-19: a call for greater medical nutrition education

In a recent Editorial,¹ *The Lancet Diabetes & Endocrinology* highlighted the burden of underlying metabolic diseases in the ongoing global health crisis of COVID-19. When facing a life-threatening condition such as COVID-19, it is important that patients have the strength and reserve to recover from the acute phase of illness while also being prepared for the likely burdensome rehabilitation phase they will face later on. In both these phases, nutrition is of paramount importance.

The Editorial notes the relationship between obesity and hospitalisation risk with COVID-19 while reporting on conditions such as diabetes, hypertension, and cardiovascular disease. All of these conditions have

strong links to both dietary patterns and lifestyle behaviours. Likewise, although lesser noted, underweight individuals are also at risk of being immunocompromised and therefore have an increased susceptibility to infections.² It is thought that there will be a multi-stage impact of COVID-19 where we would need to look at the role of nutrition in acute treatment, in recovery, and in prevention of chronic conditions that increase susceptibility to infection. Medical professionals must also consider the influence of nutrition on mental health. However, doctors and medical students are ill-equipped to assist patients in making informed nutritional decisions.

A recent publication³ highlights the pressing need for greater education on nutrition within medical curricula. It describes how more than 95% of medical students and doctors believe that doctors play a vital role in nutritional care, yet more than 70% reported that they received less than 2 h nutrition training while at medical school. The study found that lack of knowledge was the main barrier to advising patients on nutrition. Bearing in mind the paramount importance of nutrition, this is simply unacceptable.

Barriers to increased medical nutrition education include already-full teaching schedules and limited student engagement, with only 68% of students believing that there is a need for increased nutrition education within their curriculum.³ In the context of COVID-19, the importance of nutrition has only increased—we must overcome the barriers to greater medical nutrition education to improve the metabolic health of citizens.

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- 1 The Lancet Diabetes & Endocrinology. COVID-19: underlying metabolic health in the spotlight. *Lancet Diabetes Endocrinol* 2020; **8**: 457.
- 2 Dobner J, Kaser S. Body mass index and the risk of infection - from underweight to obesity. *Clin Microbiol Infect* 2018; **24**: 24–28.
- 3 Macaninch E, Buckner L, Amin P, et al. Time for nutrition in medical education. *BMJ Nutr Prev Health* 2020; published online April 16. DOI:10.1136/bmjnph-2019-000049.

Management of diabetes in patients with COVID-19

We read with interest the practical recommendations for management of diabetes in patients with COVID-19 by Stefan Bornstein and colleagues¹ in *The Lancet Diabetes & Endocrinology*. However, in the panel describing special considerations for anti-diabetic drugs, we note that two commonly used groups, sulfonylureas and pioglitazone, are missing. Of these, pioglitazone, a PPAR- γ agonist, merits further discussion because it interacts with both the mechanisms that might play a role in patients with diabetes with COVID-19, as described by Bornstein and colleagues.¹ In addition, a substantial minority of people with diabetes in the UK,² and a considerable proportion worldwide, use pioglitazone.

Pioglitazone upregulates expression of ACE2 in rat tissues,³ leading to speculation that its use might increase susceptibility to, and severity of, COVID-19, because ACE2 acts as a co-receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter the cell. However, apart from ACE2 upregulation in insulin-sensitive tissues in animals, namely the liver, adipose tissue, and skeletal muscle, there is no evidence that pioglitazone upregulates expression of

ACE2 in alveolar cells. Alternatively, as described by Bornstein and colleagues,¹ by increasing ACE2 expression in insulin-sensitive tissues, pioglitazone might help ameliorate the harmful effects of excess angiotensin II. In addition, using homology modelling and molecular docking techniques, Wu and colleagues⁴ have shown that pioglitazone is a potential inhibitor of 3-chymotrypsin-like protease, which is essential for RNA synthesis and replication of SARS-CoV-2. However, this software-based prediction of pioglitazone as a potential inhibitor of SARS-CoV-2 RNA synthesis and replication needs validation in both in-vitro and in-vivo studies.

People with diabetes and COVID-19 are at a higher risk of SARS-CoV-2-driven hyperinflammation and cytokine storm syndrome.⁵ Pioglitazone might play an important role by moderating the host inflammatory response on multiple fronts. PPAR- γ agonists decrease the secretion of various pro-inflammatory cytokines, including TNF- α , IL-1, and IL-6 in the monocytes and macrophages. Furthermore, animal studies have shown that pioglitazone can suppress TNF- α and IL-6 generation in adipose tissue. However, more research is needed to substantiate these benefits in humans.

Pioglitazone is an inexpensive anti-diabetic drug, used widely around the globe. It has the potential to do more benefit than harm, and, in our view, it can be safely continued in people with diabetes and COVID-19, except in specific conditions in which its use is not recommended, including symptomatic heart failure and liver dysfunction with significantly elevated transaminases.

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- 1 Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; **8**: 546–50.
- 2 Wilkinson S, Douglas I, Stirnadel-Farrant H, et al. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017. *BMJ Open* 2018; **8**: e022768.
- 3 Zhang W, Xu YZ, Liu Bo, et al. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. *ScientificWorldJournal* 2014; **2014**: 603409.
- 4 Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm Sini B* 2020; **10**: 766–88.
- 5 Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020; published online March 31. <https://doi.org/10.1002/dmrr.3319>.

We read with interest the recommendations on the management of diabetes in patients with COVID-19 by Stefan Bornstein and colleagues.¹ However, their suggestion of discontinuing metformin in patients with severe symptoms of COVID-19 (to reduce the risk of lactic acidosis) raises a number of issues. We believe that it is important to maintain a thoughtful approach to metformin therapy in patients with diabetes and COVID-19.

After the synthesis of the first glucose-lowering biguanides in the 1920s, metformin was rediscovered in the 1940s for the treatment of malaria. In 1949, a dimethylbiguanide preparation (flumamine) was used to treat influenza virus infections. Since then, metformin has shown adjuvant efficacy in malaria, tuberculosis, hepatitis C virus infection, and Zika virus infection, indicating that it has considerable potential as an antimicrobial. Of note, metformin is reportedly one of the drugs that targets human host factors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via the mTOR pathway.²

Metformin has direct and indirect immunosuppressive effects. In particular, metformin reduces the secretion of pro-inflammatory cytokines (IL-6, IL-1 β , CXCL1, and CXCL2) by macrophages. These cytokines are involved in the development of acute