



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

whether this low adherence reflects gastrointestinal symptoms, aversion to injections, or other factors.

Important questions remain. First, how much does GIP receptor stimulation contribute to the effects of tirzepatide? GIP has incompletely understood effects on adipose tissue, intestinal blood flow, glucagon secretion, and even bone resorption; moreover, its insulinotropic effect can be restored, in part, with fastidious glycaemic control.<sup>8</sup> Historically, the evaluation of GIP actions has been hampered by species differences, but a human GIP receptor antagonist is now available, and should be used in future mechanistic studies.<sup>9</sup> Second, does persistent slowing of gastric emptying by GLP-1 receptor stimulation contribute to the substantial reductions in postprandial glycaemia by tirzepatide? The SURPASS-3 investigators dismiss this possibility, but at least one long-acting GLP-1 receptor agonist, once-weekly exenatide, maintains a substantial effect to slow gastric emptying with sustained use.<sup>10</sup> This possibility should be evaluated for tirzepatide, and other GLP-1 receptor agonists, using the gold standard method of scintigraphy, rather than the suboptimal paracetamol absorption test.<sup>11</sup> More personalised use of peptides with GLP-1 activity will be facilitated by clarifying their effects on both gastrointestinal symptoms and gastric emptying. Finally, the positioning of tirzepatide in the therapeutic algorithm will be influenced by emerging information on cardiovascular outcomes, fatty liver disease, renal protection, and durability of effects, which is awaited with interest.

CKR reports research funding from Sanofi and Novartis, and advisory board fees from Allergan and Glyscend, outside the area of work commented on here. MH reports symposia fees from Sanofi, Eli Lilly, Boehringer Ingelheim, and AstraZeneca, outside the area of work commented on here.

Christopher K Rayner, \*Michael Horowitz  
michael.horowitz@adelaide.edu.au

Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, SA, Australia (CKR, MH); Department of Gastroenterology and Hepatology (CKR) and Endocrine and Metabolic Unit (MH), Royal Adelaide Hospital, Adelaide, SA 5000, Australia

- Holst JJ, Gribble F, Horowitz M, Rayner CK. Roles of the gut in glucose homeostasis. *Diabetes Care* 2016; **39**: 884–92.
- Rayner CK, Horowitz M. Agonism of receptors in the gut-pancreas axis in type 2 diabetes: are two better than one? *Lancet* 2018; **391**: 2577–78.
- Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* 2021; published online Aug 6. [https://doi.org/10.1016/S0140-6736\(21\)01443-4](https://doi.org/10.1016/S0140-6736(21)01443-4).
- Friás JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021; published online June 25. <https://doi.org/10.1056/NEJMoa2107519>.
- Du YT, Rayner CK, Jones KL, Talley NJ, Horowitz M. Gastrointestinal symptoms in diabetes: prevalence, assessment, pathogenesis, and management. *Diabetes Care* 2018; **41**: 627–37.
- Lean ME, Carraro R, Finer N, et al. Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. *Int J Obes (Lond)* 2014; **38**: 689–97.
- Divino V, DeKoven M, Khan FA, Boye KS, Sapin H, Norrbacka K. GLP-1 RA treatment patterns among type 2 diabetes patients in five European countries. *Diabetes Ther* 2017; **8**: 115–28.
- Mathiesen DS, Bagger JI, Bergmann NC, et al. The effects of dual GLP-1/GIP receptor agonism on glucagon secretion—a review. *Int J Mol Sci* 2019; **20**: 4092.
- Gasbjerg LS, Christensen MB, Hartmann B, et al. GIP(3-30)NH2 is an efficacious GIP receptor antagonist in humans: a randomised, double-blinded, placebo-controlled, crossover study. *Diabetologia* 2018; **61**: 413–23.
- Jones KL, Huynh LQ, Hatzinikolas S, et al. Exenatide once weekly slows gastric emptying of solids and liquids in healthy, overweight people at steady-state concentrations. *Diabetes Obes Metab* 2020; **22**: 788–97.
- Horowitz M, Rayner CK, Marathe CS, Wu T, Jones KL. Glucagon-like peptide-1 receptor agonists and the appropriate measurement of gastric emptying. *Diabetes Obes Metab* 2020; **22**: 2504–06.

## What is the association of COVID-19 with heart attacks and strokes?



It has been known for several decades that there is a transient increase in the risk of myocardial infarction and stroke in association with influenza, pneumonia, acute bronchitis, and other chest infections.<sup>1-4</sup> It is against this background that Ioannis Katsoularis and colleagues<sup>5</sup> studied a possible association of these conditions with COVID-19 during the first wave of the pandemic in Sweden, between February and September, 2020, which they report in *The Lancet*. The study linked data from the national registers for outpatient and inpatient clinics and the cause of death

register for all 86742 people (median age 48 years [IQR 31–62]; 37235 [43%] male, 49507 [57%] female) with COVID-19 who were reported to SmiNet (Swedish Public Health Agency) and 348481 matched controls. Two analysis methods were used to assess the association of COVID-19 with the risk of acute myocardial infarction and of ischaemic stroke. First, the investigators used the self-controlled case series (SCCS) method to compare incidence rate ratios (IRRs) for first acute myocardial infarction and ischaemic stroke before and after patients were determined to have COVID-19. Second, they used a

Published Online  
July 29, 2021  
[https://doi.org/10.1016/S0140-6736\(21\)01071-0](https://doi.org/10.1016/S0140-6736(21)01071-0)  
See [Articles](#) page 599



FC Trade/Getty Images

matched cohort study to compare the odds of an acute myocardial infarction or ischaemic stroke in the 14 days following onset of COVID-19 with control individuals who did not have a diagnosis of COVID-19 and who were similar in age, sex, and region, with additional adjustment for comorbid disease, income, education, and country of birth.<sup>5</sup>

Because the actual date of infection was unknown, the researchers defined the closest available surrogate (the date of COVID-19 symptom onset, SARS-CoV-2 sample date, or the date of the relevant clinic visit or hospital admission), and denoted it as day 0. There was a large peak of both acute myocardial infarctions and ischaemic strokes recorded on day 0. If day 0 was excluded, the risks of acute myocardial infarction were about three times higher in the first few weeks after COVID-19, irrespective of the study method (IRR 2.89 [95% CI 1.51–5.55] in the first week and 2.53 [1.29–4.94] in the second week after day 0 in the SCCS study, and odds ratio [OR] 3.41 [95% CI 1.58–7.36] in the first 2 weeks in the matched cohort study). If day 0 was included, the risks of acute myocardial infarction were much higher (IRR 8.44 [95% CI 5.45–13.08] in the first week and 2.56 [1.31–5.01] in the second week after day 0 in the SCCS study, and OR 6.61 [95% CI 3.56–12.20] in the first 2 weeks in the matched cohort study). Similarly, COVID-19 was associated with a three times higher risk of ischaemic stroke when day 0 was excluded (IRR 2.97 [95% CI 1.71–5.15] in the first week and 2.80 [1.60–4.88] in the second week after day 0 in the SCCS study, and OR 3.63 [95% CI 1.69–7.80] in the first 2 weeks in the matched cohort study). Again, the risks were much higher when day 0 was included (IRR 6.18 [95% CI 4.06–9.42] in the first week and 2.85 [1.64–4.97] in the second week after day 0 in the SCCS study, and OR 6.74 [95% CI 3.71–12.20] in the first 2 weeks in the matched cohort study).

How should these results be interpreted, and what are their implications for the management of patients with COVID-19? The most important consideration is the potential for bias. Why is there such a striking peak of myocardial infarction and stroke on day 0? Such a peak could occur if COVID-19 is a potent cause of myocardial infarction and stroke, events that in turn lead patients to seek medical help, but it could also occur if patients presenting with such a condition were more likely to be tested for SARS-CoV-2 than those without symptoms suggestive of such a diagnosis (ie, a test bias). Excluding

day 0 removes the potential for test bias, but might lead to an underestimate of the true risks of myocardial infarction and stroke secondary to COVID-19.

If there is indeed a moderately increased risk of myocardial infarction and stroke secondary to COVID-19, then why was there a 30–40% fall in admissions for both acute coronary syndromes<sup>6,7</sup> and stroke<sup>8,9</sup> during the first wave of the pandemic? The answer is that any possible attributable excess due to COVID-19 was far smaller than the numbers of people who did not seek medical attention for symptoms of acute coronary syndrome or stroke during this period. For myocardial infarction, for example, during the period from February to mid-September, 2020, there were 381 000 confirmed cases of COVID-19 in the UK.<sup>10</sup> The estimated excess attributable risk due to COVID-19 in the present study was 0.02%,<sup>5</sup> which, if it had been observed in the UK, would have caused about 76 additional myocardial infarctions, as compared with approximately 5000 people who might not have presented to hospital with myocardial infarction during the first wave of the pandemic.<sup>6</sup>

It seems reasonable to infer that the persistence of risk for several weeks after SARS-CoV-2 infection is consistent with COVID-19 causing an increased risk of thrombo-occlusive disease, as has been reported for other respiratory infections.<sup>1–4</sup> The absolute risks are small, but further studies are needed to evaluate the time course of increased cardiovascular risk in patients with COVID-19 and to investigate possible mechanisms. However, it is important to keep in mind that the excess risks of myocardial infarction and stroke in a person with COVID-19 are substantially smaller than those resulting from respiratory failure.

MM reports grants and non-financial support from The Medicines Company/Novartis and Novo Nordisk, unrelated to the topic of this Comment. CB reports grants from Boehringer Ingelheim, the Medical Research Council, the British Heart Foundation, and the National Institute for Health Research, all unrelated to the topic of this Comment.

**Marion Mafham, \*Colin Baigent**  
colin.baigent@ndph.ox.ac.uk

Clinical Trial Service Unit Nuffield Department of Population Health, Oxford, UK (MM); MRC Population Health Research Unit, Nuffield Department of Population Health, Oxford OX3 7LF, UK (CB)

- 1 Warren-Gash C, Hayward AC, Hemingway H, et al. Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study. *J Infect Dis* 2012; **206**: 1652–59.
- 2 Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004; **351**: 2611–18.
- 3 Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med* 2018; **378**: 345–53.

- 4 Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. *Eur Heart J* 2008; **29**: 96–103.
- 5 Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly A-M. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet* 2021; published online July 29. [https://doi.org/10.1016/S0140-6736\(21\)00896-5](https://doi.org/10.1016/S0140-6736(21)00896-5).
- 6 Mafham MM, Spata E, Goldacre R, et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet* 2020; **396**: 381–89.
- 7 Solomon MD, McNulty EJ, Rana JS, et al. The COVID-19 pandemic and the incidence of acute myocardial infarction. *N Engl J Med* 2020; **383**: 691–93.
- 8 Tejada Meza H, Lambea Gil Á, Saldaña AS, et al. Impact of COVID-19 outbreak on ischemic stroke admissions and in-hospital mortality in North-West Spain. *Int J Stroke* 2020; **15**: 755–62.
- 9 D'Anna L, Brown M, Oishi S, et al. Impact of national lockdown on the hyperacute stroke care and rapid transient ischaemic attack outpatient service in a comprehensive tertiary stroke centre during the COVID-19 pandemic. *Front Neurol* 2021; **12**: 627493.
- 10 Our World in Data. United Kingdom: coronavirus pandemic country profile. <https://ourworldindata.org/coronavirus/country/united-kingdom> (accessed April 26, 2021).

## Parental education's role in child survival

The end of the Millennium Development Goals era marked progress in global under-5 mortality, but this was largely inequitable.<sup>1</sup> Since the introduction of the Sustainable Development Goals (SDGs) much evidence has indicated the necessity of an integrative and intersectoral approach to the global health agenda.<sup>2–4</sup> In recognition of this, education has been considered a core social determinant of health, with SDG 4 focusing on ensuring inclusive and equitable quality education and promoting lifelong learning opportunities for all, with an explicit indicator on better education for girls.

Evidence shows the positive relationship between parental education and child health indicators, and in particular the contribution of maternal education to declines in child mortality.<sup>5,6</sup> Pathways include economic empowerment, health literacy, health-care-seeking behaviours, working conditions, family structure, and provision of opportunities for quality early childhood development and education.<sup>7,8</sup> Maternal education potentially results in the acquisition of literacy skills, economic independence, and independent decision making, leading to improved health-care-seeking behaviour that consequently can improve health-care and vaccination coverage among children and reduced burden of childhood diseases and mortality.<sup>9–11</sup>

In *The Lancet*, Mirza Balaj and colleagues report their comprehensive global systematic review and meta-analysis that estimated the total reductions in under-5 mortality associated with increased maternal and paternal education.<sup>12</sup> 300 studies from 92 countries were synthesised, including data from 114 Demographic and Health Surveys (DHS), published between 1982 and 2020, capturing 3 112 474 livebirths. The authors implemented novel mixed-effects meta-regression models to address

heterogeneity in referent and exposure measures among the studies and to adjust for study-level covariates (wealth or income, partner's years of schooling, and sex of the child). This study quantified the transgenerational importance of parental education for child survival, suggesting a global dose–response relationship between increased maternal and paternal education and greater survival at all ages under 5 years. Balaj and colleagues reported a reduction in under-5 mortality of 31·0% (95% CI 29·0–32·6) for children born to mothers with 12 years of education and 17·3% (15·0–18·8) for children born to fathers with 12 years of education, compared with those born to a parent with no education. Moreover, adding a single year of schooling was, on average, associated with a reduction in under-5 mortality of 3·04% (2·82–3·23) for maternal education and 1·57% (1·35–1·72) for paternal education. Balaj and colleagues suggest that maternal education was a stronger predictor of under-5 mortality than was paternal education for children across all age groups. They conclude that both lower maternal and paternal education are risk factors for child mortality, even after controlling for other markers of family socioeconomic status that can influence child health, including wealth or income, partner's years of schooling, and sex of the child.

Notwithstanding the evidence, this study has highlighted some limitations and crucial data gaps to consider while interpreting the findings, as well as for future research. First, the findings are based on ecological snapshots from the DHS and other data sources that carry inherent data limitations, including availability and quality of the variables reported. Consequently, some important variables such as health-care coverage, immunisation rates, nutrition indicators, and burden of infectious



Andrew Atchison/Getty Images

Published Online  
June 10, 2021  
[https://doi.org/10.1016/S0140-6736\(21\)00787-X](https://doi.org/10.1016/S0140-6736(21)00787-X)  
See [Articles](#) page 608