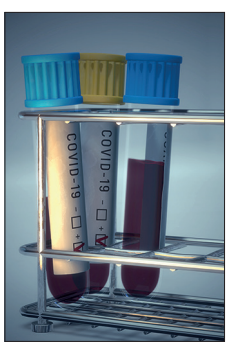
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

7 Camargo CA, Sluyter J, Stewart AW, et al. Effect of monthly high-dose vitamin D supplementation on acute respiratory infections in older adults: a randomized controlled trial. *Clin Infect Dis* 2020; **71:** 311–17.
8 Ganmaa D, Uyanga B, Zhou X, et al. Vitamin D supplements for prevention of tuberculosis infection and disease. *N Engl J Med* 2020; **383:** 359–68.
9 Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010; **303:** 1815–22.
10 Appel LJ, Michos ED, Mitchell CM, et al. The effects of four doses of vitamin D supplements on falls in older adults: a response-adaptive, randomized clinical trial. *Ann Intern Med* 2020; published online Dec 1. https://doi.org/10.7326/M20-3812.

Observational research on severe COVID-19 in diabetes



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Older age is by far the strongest risk factor for severe COVID-19, followed by deprivation, non-white ethnicity, male sex, and chronic medical conditions.[1] Such information can guide protection and vaccination strategies, and can provide leads for causal inference and development of novel treatments.

However, in seeking to define risk factors for severe COVID-19, scientific thoroughness has often lost out to superficial newsworthiness. There has been a huge increase in the use of preprint servers, with media coverage preceding peer review and unparallelled fast-tracking of COVID-19 reports. Many reports have lacked careful epidemiologic design, conduct, and analysis.[2] For example, many small studies with few clinical events have reported strong associations that—in view of unavoidable publication bias—are likely to be spurious.[2] Additionally, hospitalisation and critical care unit admission are biased markers of severe COVID-19 because they are subject to hospitalisation and critical care unit admission policies.

That older age and chronic medical conditions increase risk of severe COVID-19 is clinical common sense. More detailed information is needed, but it is imperative that such information be scientifically robust, because the social implications of scientific information during a pandemic need to be carefully considered. Pandemics threaten societies; societies respond by seeking causes but also by apportioning blame.[3] Type 2 diabetes and obesity are a case in point. Both are associated with stigma and untenable but harmful assumptions (eg, that they are caused by insufficient self-control), not only by the lay public, but also by health-care professionals.[4] Indeed, the UK government recently suggested that people should lose weight to "reduce pressure on doctors and nurses in the NHS [National Health Service], and free up their time to treat other sick and vulnerable patients", which is a glaring example of a health promotion strategy that draws on guilt and shame.[3] I would add only that there is no evidence whatsoever that any such strategy is effective.

In this context, McGurnaghan and colleagues investigated to what extent diabetes and associated conditions determine risk of severe COVID-19 in Scotland.[5] This study is important because COVID-19 appears to hit hard among people with diabetes. In an English nationwide study,[6] a third of all in-hospital deaths during the first wave of the pandemic occurred in people with diabetes. The Scottish study, also nationwide, avoided many of the epidemiological pitfalls I have referred to. Severe COVID-19 was defined as fatal or critical care unit-treated COVID-19 during the first wave of the pandemic. The addition of critical care unit-treated COVID-19 is subject to admission bias, but these survivors represented a minority (119 [11%] of 1082 people with diabetes who developed fatal or critical care unit-treated COVID-19), and the results were similar when these cases were excluded. Severe COVID-19 and potential determinants were investigated by impressively leveraging existing databases that cover virology testing, hospitalisations and discharges, critical care, and deaths thought to be related to COVID-19; these databases were then combined with a community health index and a national diabetes register with detailed clinical data. Odds ratios (ORs) for severe COVID-19, as compared with no diabetes, were 2·4 for type 1 diabetes and 1·4 for type 2 diabetes, a difference mostly explained by differences in diabetes duration. A prediction model for severe COVID-19 had a C-statistic of 0·76 for age, sex, and diabetes type and duration, and 0·85 when 11 other variables were added (care home residency, deprivation index, number of hospital admissions in the past 5 years, neurological comorbidities, HbA_{1c}, BMI, estimated glomerular filtration rate, systolic blood pressure, use of any antihypertensive, and number of diabetes and other drug classes used). As the authors note, a C-statistic of 0·85 means that, faced with a case and non-case pair, the

prediction model would correctly assign the case as being at higher risk 85% of the time.

The study's main limitations were that it could not assess non-white ethnicity, because of Scotland's demographics, and that the prediction model was not externally validated. Nevertheless, the model makes sense in that many of the variables included plausibly reflect an individual's vulnerability to severe COVID-19. Additionally, the overall conclusions were broadly similar to those of studies conducted in England, in which non-white ethnicity was also a risk factor.[6,7]

The model was developed for prediction, not causal inference. In a prediction model, variables that can be reliably assessed (such as previous hospitalisations or BMI) will tend to dominate, as they are less subject to regression dilution than variables that have greater measurement error (such as blood pressure). However, the inclusion of a variable in a prediction model should not be confused with biological importance.

More insight into the mechanisms leading to severe COVID-19 is urgently needed. The risk conferred by diabetes is probably related in part to hyperglycaemia, which impairs host defences, but the role of other factors—such as specific antihyperglycaemic drugs, in-hospital metabolic decompensation, and increased coagulation activity—remains to be defined.[8] It is noteworthy that even mildly decreased estimated glomerular filtration rate is a strong risk factor for severe COVID-19.[5,7] More insight is also needed into the roles of ethnicity, high blood pressure (which is surprisingly associated with reduced risk[1,5,7]) and current smoking (which is either not associated[5] or, counterintuitively, associated with reduced risk[1,7]). BMI appears non-linearly associated with risk, with nadirs reported at around 30 kg/m² or 25·0–29·9 kg/m².[5,7] Such a pattern, if causal, suggests complex biology. Regardless, all these associations are subject to bias through residual or unmeasured confounding, or overadjustment. For example, obesity is associated with low vitamin D status, which itself might increase risk.

As long as more precise data are not available, the model developed by McGurnaghan and colleagues[5] might be helpful to guide vaccination and protection policies. Although causal inferences should be resisted, some measures appear prudent, such as improvement of protection in residential care facilities, careful management of hyperglycaemia and comorbidities, medication reviews, and—notwithstanding the mixed findings—smoking cessation.

I declare no competing interests.

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1 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.
2 Selvin E, Juraschek SP. Diabetes epidemiology in the COVID-19 pandemic. *Diabetes Care* 2020; **43:** 1690–94.
3 The Lancet Diabetes and Endocrinology. Obesity and COVID-19: blame isn't a strategy. *Lancet Diabetes Endocrinol* 2020; **8:** 731.
4 O'Keeffe M, Flint SW, Watts K, Rubino F. Knowledge gaps and weight stigma shape attitudes toward obesity. *Lancet Diabetes Endocrino* 2020; **8:** 363–65.
5 McGurnaghan SJ, Weir A, Bishop J, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. *Lancet Diabetes Endocrinol* 2020; published online Dec 23. https://doi.org/10.1016/S2213-8587(20)30405-8
6 Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020; **8:** 813–22.
7 Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020; **8:** 823–33.
8 Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020; **8:** 782–92.

Challenges in investigating risk factors for thyroid cancer

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Thyroid cancer has become the fifth most commonly diagnosed cancer in adult women worldwide, and the second most common in women older than 50 years.[1] The rapid increase in incidence compared with mortality trends—which generally have remained stable at low levels (around two orders of magnitude lower than incidence) or have even declined[2]—strongly suggests that the thyroid cancer epidemic has been largely driven by overdiagnosis (the diagnosis of cancers that would not have caused symptoms in a person's lifetime).[3] The increasingly intense scrutiny of the thyroid gland has led to the discovery of a large reservoir of subclinical thyroid cancers.[4] Overdiagnosis might account for as much as 70–90% of all thyroid cancer diagnosed in adult women in some countries including South Korea, the USA, and Italy, and around 40–60% in the Nordic countries—in which there has been a smaller increase in thyroid cancer incidence