evidence of differences in anti-fracture efficacy between zolendronate and denosumab, despite the slightly larger effects of denosumab on BMD.\(^6,7\) Thus, absence of trials directly measuring fractures could lead to inappropriate preferences in use of available drugs.

The study by Black and colleagues is a landmark in data synthesis and will be a valuable resource to address many future questions, but it might not herald the end of large trials in osteoporosis drug development.

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60 years on, growth hormone inches its way to safety

Endocrinology is a specialty in which a substantial number of disorders that affect the component parts of the system primarily reduce quality of life rather than the length of survival. Furthermore, given that therapy is available for most endocrine disorders, a careful balance has to be achieved between perceived benefit of therapy and safety. The treatment of children with short stature with growth hormone is a prime example.

From the first positive evidence of a species-specific beneficial effect of growth hormone in children in 1958,\(^1\) national programmes using human pituitary-derived growth hormone, obtained from cadavers, were gradually introduced and shown to be effective in improving the stature of children considered to be growth hormone deficient. However, in 1985 it became clear that some of these children had acquired Creutzfeldt-Jacob disease from the human pituitary-derived growth hormone,\(^2\) thereby terminating the therapeutic use of this source of growth hormone. Within a year, recombinant DNA-derived human growth hormone was available and in clinical use. This switch in the type of growth hormone for therapy had implications beyond safety.

Given that the availability of recombinant human growth hormone was limitless, and given the knowledge that individuals with pituitary gigantism exceed their genetic height destiny through an excess of growth hormone, it follows that almost any short child, not just those who are growth hormone deficient, might achieve a greater height if treated with growth hormone. This possibility expanded clinical practice—therapy was no longer replacing a missing hormone, but treating a (potential) adverse quality of life indication (short stature). Consequently, various disorders that might cause short stature in children were approved as indications for growth hormone therapy in several countries, including chronic renal failure, Turner Syndrome, achondroplasia, small for gestational age, idiopathic short stature, SHOX haploinsufficiency, and Noonan syndrome.\(^3\)

Given the broadening use of growth hormone in children, from physiological replacement to pharmacology, and the treatment of several growth disorders that inherently carried an increased risk of serious complications, safety concerns heightened, the most serious of which were over malignancy and vascular disease. However, no conclusive evidence existed to indicate that growth hormone therapy in childhood induced de novo malignancy,\(^4\) nor that children with radiation-induced growth hormone deficiency after childhood malignancy treatment were at increased risk of tumour recurrence when treated with growth hormone replacement.\(^5\) However, to provide information about mortality and vascular risk, large numbers and lengthy follow-up were needed.

Most recombinant human growth hormone safety data in the early years of follow-up were contained in

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Comment

Obesity and COVID-19: a call for action from people living with obesity

Data from France and the UK have showed a disproportionately higher prevalence of obesity in patients with COVID-19 admitted to Intensive Care Units (ICUs) compared with general population data.1 2 About 10% of ICU patients in the UK have a BMI of 40 kg/m² or more, and evidence shows increased mortality among this group.3 The UK Government advice for those with a BMI of at least 40 kg/m² is to be particularly stringent in following social distancing measures. This message has created confusion and fear among many people living with obesity because of uncertainty about their risk or what actions they should take, including people with a BMI of 30 kg/m² or more, who are also over-represented in ICU but not listed as at risk.3

We consulted with people living with obesity and summarise in this Comment the main reflections, formulated into a call for action (appendix pp 2–5). It is a candid account of the impact of COVID-19 during the peak of the pandemic in the UK. The reported effects were both physical and mental, and are likely to have a lasting impact for many years.

Overwhelmingly, we heard of genuine, all-consuming fears of contracting COVID-19, with many people afraid of not getting medical support if they were admitted to various predisposing underlying disorders in susceptible children, recombinant human growth hormone therapy, and mortality risk. Additionally, with larger numbers and longer follow-up, the CIs around the safety statements will hopefully be narrowed.

The balance between benefit and safety for recombinant human growth hormone therapy for short stature has contrasting time constraints. Benefit, in terms of final height gain, can be estimated using a prediction model1 after a few years of therapy, but safety requires decades of follow-up.

I declare no competing interests.

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See Online for appendix

databases kept by pharmaceutical companies. To gather detailed long-term safety data in a comprehensive broad-based fashion, a group of eminent paediatric endocrinologists set up a European consortium (Safety and Appropriateness of Growth hormone treatments in Europe [SAGhE]) that involved eight countries (Belgium, France, Germany, Italy, the Netherlands, Sweden, Switzerland, and the UK) and merged datasets on around 24 000 young adults treated with recombinant human growth hormone during childhood and adolescence.4 In The Lancet Diabetes & Endocrinology, Lars Sävendahl and colleagues5 present the first large international population-based cohort study of patients treated with recombinant human growth hormone during childhood. The study reports overall and cause-specific mortality data for all eight participating SAGhE countries, with more than 400 000 patient-years and up to 25 years of follow-up. All-cause mortality data only showed increased mortality in children with an inherent increased mortality risk due to their underlying disorder, whereas in patients who did not have any such predisposing disorder, overall mortality was not increased. The authors found no association between mortality and recombinant human growth hormone dose, irrespective of risk at the outset of treatment.

These findings are reassuring, both for clinicians and the families of those treated with recombinant human growth hormone during childhood. Further analysis is required to explore the interaction between