with the original virus or the alpha variant as compared with the omicron-primed cohort, the adjusted hazard ratio for infection was 0.59 (95% CI, 0.40 to 0.85) (Fig. 1B).

In the first 70 days of follow-up, when infections were dominated by the BA.2 subvariant,[2,3] the adjusted hazard ratio for infection was 0.92 (95% CI, 0.51 to 1.65). However, the cumulative incidence curves diverged when the BA.4 and BA.5 subvariants were introduced and subsequently dominated[4] (adjusted hazard ratio, 0.46; 95% CI, 0.34 to 0.62) (Fig. 1A).

Limitations of the study are discussed in Section S1. One potential limitation was the difference in the frequencies of testing between the two cohorts, but a sensitivity analysis with adjustment for these differences showed results similar to those in the main analysis.

Omicron infection induces strong protection against a subsequent omicron infection.[2,4] In the present cohort study, an additional, earlier infection with non-omicron SARS-CoV-2 was found to strengthen this protection against a subsequent omicron infection. The earlier pre-omicron infection may have broadened the immune response against a future reinfection challenge.

Hiam Chemaitelly, Ph.D.

Weill Cornell Medicine–Qatar
Doha, Qatar
hsc2001@qatar-med.cornell.edu

Roberto Bertollini, M.D., M.P.H.

Ministry of Public Health
Doha, Qatar

Laith J. Abu-Raddad, Ph.D.

Weill Cornell Medicine–Qatar
Doha, Qatar
lja2002@qatar-med.cornell.edu

and Others

A complete list of authors is available with the full text of this letter at NEJM.org.

Supported by the Biomedical Research Program and the Biostatistics, Epidemiology, and Biomathematics Research Core at Weill Cornell Medicine–Qatar; the Qatar Ministry of Public Health; Hamad Medical Corporation; and Sidra Medicine. The Qatar Genome Program and Qatar University Biomedical Research Center supported viral genome sequencing.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on October 12, 2022, at NEJM.org.

1. Reynolds CJ, Pade C, Gibbons JM, et al. Immune boosting by B.1.1.529 (omicron) depends on previous SARS-CoV-2 exposure. Science 2022;377(6603):eabq1841.
2. Chemaitelly H, Ayoub HH, Coyle P, et al. Protection of omicron sub-lineage infection against reinfection with another omicron sub-lineage. Nat Commun 2022;13:4675.
3. Altarawneh HN, Chemaitelly H, Ayoub HH, et al. Effects of previous infection and vaccination on symptomatic omicron infections. N Engl J Med 2022;387:21-34.
4. Altarawneh HN, Chemaitelly H, Ayoub HH, et al. Protective effect of previous SARS-CoV-2 infection against omicron BA.4 and BA.5 subvariants. N Engl J Med 2022;387:1620-2.

DOI: 10.1056/NEJMc2211055

Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes

TO THE EDITOR: In the GEMS trial, Crowther and colleagues (Aug. 18 issue)[1] conclude that applying lower glycemic thresholds for the diagnosis of gestational diabetes (as advised by the World Health Organization [WHO]) doubled the number of diagnoses of this disorder without any reduction in the number of infants who were large for their gestational age. Of the 4061 pregnant women who were enrolled in the trial, 3688 (90.8%) met either the lower or higher glycemic criteria. Only 373 women in the trial were in a subgroup with results that fell between the two criteria. In this discordant group, treatment resulted in better perinatal outcomes than routine care. This finding suggests that there is a difference in outcomes between the high and low diagnostic thresholds. The trial was not powered or designed to detect differences among women with glucose values between the two thresholds, so the value of the negative finding of the trial is not clear. Trials that are specifically designed to assess effects among patients with glucose values between the lower and higher glycemic thresholds could resolve this issue and help to guide future policy decisions.[2]

Rebecca C. Painter, M.D., Ph.D.

Amsterdam UMC
Amsterdam, the Netherlands
r.c.painter@amc.uva.nl

Bas B. van Rijn, M.D., Ph.D.

Erasmus MC
Rotterdam, the Netherlands

Patrick M.M. Bossuyt, Ph.D.

Amsterdam UMC
Amsterdam, the Netherlands

No potential conflict of interest relevant to this letter was reported.

1. Crowther CA, Samuel D, McCowan LME, et al. Lower versus higher glycemic criteria for diagnosis of gestational diabetes. N Engl J Med 2022;387:587-98.
2. Bossuyt PM, Lijmer JG, Mol BW. Randomised comparisons of medical tests: sometimes invalid, not always efficient. Lancet 2000;356:1844-7.

DOI: 10.1056/NEJMc2212585

TO THE EDITOR: In the GEMS trial, Crowther et al. report that the use of lower glycemic criteria for the diagnosis of gestational diabetes did not result in a lower risk of large-for-gestational-age birth (the primary outcome) than the use of higher glycemic criteria in the two trial groups. However, the use of lower glycemic criteria appeared to be highly effective in the subgroup of patients who had intermediate levels of hyperglycemia and were randomly assigned to either the intervention or control group.

The apparent contradiction may be explained by statistical power. Approximately 9% of the women fell into the intermediate subgroup, and their risk of a primary-outcome event in the absence of treatment was approximately doubled, which resulted in a population-attributable fraction of less than 10%. If we assume that treatment completely reduced the excess risk of a primary-outcome event, the study had less than 20% power to detect a relative 10% difference between the two groups. The attributable fraction within the subgroup was approximately 50%, and the power to detect a relative 50% decrease in the primary outcome with treatment within the subgroup was approximately 70%. This observation is consistent with the findings of a previous analysis that compared different study designs for screening.[1] Studies in which participants are randomly assigned to undergo screening as compared with no screening require larger sample sizes than studies in which all participants are screened and those who are at high risk are randomly assigned to the intervention group or the control group.

Gordon C.S. Smith, D.Sc.
Ulla Sovio, Ph.D.

University of Cambridge
Cambridge, United Kingdom
gcss2@cam.ac.uk

Dr. Smith reports receiving research support from Roche Diagnostics, Illumina, and Sera Prognostics; receiving lecture fees that were paid to her department from Roche; receiving consulting fees from GSK; and being a member of a data monitoring committee for trials of a vaccine against respiratory syncytial virus during pregnancy from GSK. No other potential conflict of interest relevant to this letter was reported.

1. Smith GC. Researching new methods of screening for adverse pregnancy outcome: lessons from pre-eclampsia. PLoS Med 2012;9(7):e1001274.

DOI: 10.1056/NEJMc2212585

TO THE EDITOR: Crowther et al. aimed to determine whether defining and treating gestational diabetes at a lower-than-usual glycemic level would prevent large-for-gestational-age births. The authors provide the results of two analyses with very different implications. In the intention-to-treat analysis, which is described in the abstract and conclusions, the result is of little value because it is dominated by outcomes from the 91% of the women (mostly euglycemic) whose care was unaffected by their randomized assignment. Thus, it is predictable that this analysis would show little between-group difference in outcomes. The appropriate patients, who were evaluated in their alternative analysis, are those with glycemic levels that would be diagnosed and treated in one of the trial groups but not in the other. This analysis showed an impressive adjusted relative risk of 0.33 for large-for-gestational-age birth. However, it should be clarified whether the patients were analyzed according to their randomized assignments or, as stated, according to their receipt of treatment. If the former is correct, the case for a detailed assessment of developmental outcomes in the infants would be enhanced.

George G. Rhoads, M.D., M.P.H.

Rutgers University
Piscataway, NJ
rhoads7@gmail.com

No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc2212585

TO THE EDITOR: In their report on the use of lower or higher glycemic criteria for the diagnosis of gestational diabetes, Crowther et al. found that the use of a lower cutoff for the fasting plasma glucose level (≥92 mg per deciliter) did not result in a lower risk of large-for-gestational-age birth than the use of a higher cutoff (≥99 mg per deciliter). We have shown that the risk of large-for-gestational-age birth was nonsignificantly higher among women with a fasting plasma glucose level of 92 to 100 mg per deciliter than among those in a control group with a lower level (odds ratio, 1.37; 95% confidence interval [CI], 0.80 to 2.35) but was significantly higher among women with a fasting plasma glucose level of more than 100 mg per deciliter (odds ratio, 1.87; 95% CI, 1.04 to 3.35).[1] Therefore, it would be useful to evaluate outcomes in women in whom gestational diabetes was diagnosed according to a fasting plasma glucose level of less than 92 mg per deciliter as compared with those who had a level of 92 mg per deciliter or more.

Viswanathan Mohan, M.D., D.Sc.
Ranjit Unnikrishnan, M.D.
Ranjit M. Anjana, M.D., Ph.D.

Madras Diabetes Research Foundation
Chennai, India
drmohans@diabetes.ind.in

No potential conflict of interest relevant to this letter was reported.

1. Bhavadharini B, Anjana RM, Deepa M, et al. Association between number of abnormal glucose values and severity of fasting plasma glucose in IADPSG criteria and maternal outcomes in women with gestational diabetes mellitus. Acta Diabetol 2022;59:349-57.

DOI: 10.1056/NEJMc2212585

THE AUTHORS REPLY: In the GEMS trial, we compared the use of lower glycemic thresholds recommended by the WHO[1,2] for the diagnosis of gestational diabetes with higher thresholds that are used in New Zealand.[3] We reported findings at both the population level and in patients with mild gestational diabetes who were treated differently according to their randomized assignment. It is important to have robust evidence about both of these groups, and the findings are highly relevant for pregnant women and their families, health professionals, and policymakers.

The trial compared two sets of diagnostic criteria that are commonly used in current practice to evaluate both fasting and postprandial plasma glucose levels to detect gestational diabetes. However, we did not prespecify a comparison between two different fasting blood glucose levels, as suggested by Mohan et al. Because patients were recruited into the trial groups on the basis of the same inclusion criteria, similar distributions in baseline characteristics (including plasma glucose levels) were expected in this large trial.

At the population level, the lack of between-group difference in the primary outcome of large-for-gestational-age birth was indeed dominated by the 91% of the trial population whose care was unchanged by their group assignment, as noted by Rhoads. Nevertheless, the findings that more women in the lower-threshold group underwent induced labor, received pharmacologic agents for hyperglycemia and treatment by the diabetes services, and delivered infants who were more likely to receive treatment for hypoglycemia were driven by differences in the subgroup of women with mild gestational diabetes who were treated differently according to their randomized assignment. We agree that follow-up of mothers who participated in the trial and their children is important.

The evidence for benefit that we found using the lower diagnostic threshold in the subgroup is scientifically sound. The baseline characteristics of women with mild gestational diabetes, whose care differed according to their randomized assignment, were balanced between the trial groups (Table S2 in the Supplementary Appendix of the article, available with the full text at NEJM.org). In addition, the reduction in the incidence of large-for-gestational-age birth and other relevant health outcomes were both statistically and clinically significant in favor of the lower criteria (Table S1). We agree with the need for additional randomized trials at the subgroup level to assess all relevant benefits and risks, as recommended by Painter et al. and by Smith and Sovio. Such findings would be valuable specifically in patients with blood glucose levels between the lower and higher glycemic thresholds that were used in our trial. Moreover, it would be

important to ensure that patients and staff members were unaware of trial-group assignments.

Caroline A. Crowther, M.D.

University of Auckland
Auckland, New Zealand
c.crowther@auckland.ac.nz

Thach Tran, Ph.D.

University of Technology
Sydney, NSW, Australia

Since publication of their article, the authors report no further potential conflict of interest.

1. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. 2013 (https://apps.who.int/iris/handle/10665/85975).
2. The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002.
3. Ministry of Health. Screening, diagnosis and management of gestational diabetes in New Zealand: a clinical practice guideline. 2014 (https://www.health.govt.nz/system/files/documents/publications/screening-diagnosis-management-of-gestational-diabetes-in-nz-clinical-practive-guideline-dec14-v2.pdf).

DOI: 10.1056/NEJMc2212585

Teclistamab in Relapsed or Refractory Multiple Myeloma

TO THE EDITOR: Moreau and colleagues (August 11 issue)[1] found that, in patients with relapsed or refractory myeloma, treatment with teclistamab, a T-cell–redirecting bispecific antibody that targets CD3 on T cells and B-cell maturation antigen (BCMA) expressed on myeloma cells, resulted in a high overall response of 63.0% and a median progression-free survival of 11.3 months (95% confidence interval, 8.8 to 17.1). In addition, they found a correlation between the percent change from baseline in serum levels of soluble BCMA and response. However, we would appreciate the authors clarifying whether high levels of soluble BCMA at baseline were associated with lower efficacy, which would have direct clinical implications and may open additional perspectives. Soluble BCMA is caused by γ-secretase activity.[2] Analyses of preclinical and clinical data have shown that γ-secretase inhibitors can prevent shedding of BCMA, increase the density of BCMA on myeloma cells, decrease the concentrations of soluble BCMA, and potentially enhance the activity of therapy involving BCMA-directed chimeric antigen receptor (CAR) T cells.[3] Similarly, there is evidence in support of combining γ-secretase inhibitors with other BCMA-directed therapies, such as antibody–drug conjugates or bispecific antibodies.[4,5]

Elif Hindié, M.D., Ph.D.

Bordeaux University Hospital
Bordeaux, France
elif.hindie@chu-bordeaux.fr

No potential conflict of interest relevant to this letter was reported.

1. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med 2022;387:495-505.
2. Laurent SA, Hoffmann FS, Kuhn P-H, et al. γ-Secretase directly sheds the survival receptor BCMA from plasma cells. Nat Commun 2015;6:7333.
3. Pont MJ, Hill T, Cole GO, et al. γ-Secretase inhibition increases efficacy of BCMA-specific chimeric antigen receptor T cells in multiple myeloma. Blood 2019;134:1585-97.
4. Nooka AK, Weisel K, van de Donk NWCJ, et al. Belantamab mafodotin in combination with novel agents in relapsed/refractory multiple myeloma: DREAMM-5 study design. Future Oncol 2021;17:1987-2003.
5. Chen H, Yu T, Lin L, et al. γ-Secretase inhibitors augment efficacy of BCMA-targeting bispecific antibodies against multiple myeloma cells without impairing T-cell activation and differentiation. Blood Cancer J 2022;12:118.

DOI: 10.1056/NEJMc2211969

TO THE EDITOR: In their phase 1–2 trial of teclistamab, a T-cell–redirecting bispecific antibody that targets both CD3 and BCMA, Moreau et al. found a high rate of response in patients with refractory multiple myeloma. The flip side of drug therapy that so effectively targets plasma cells is immunosuppression: 44.8% of the patients in this trial had grade 3 or 4 infections. Only 3 deaths were attributed by investigators to teclistamab therapy, yet there were at least 19 deaths (11%) from infection. We recognize that multiply relapsed myeloma is itself a risk factor for infection,[1] but we seek clarification as to why only a small fraction of these deaths were attributed to teclistamab therapy.

As therapies for patients with myeloma become increasingly potent, we should consider their most appropriate duration; could a fixed course of therapy reduce the risk of toxic effects and maximize quality of life while maintaining or even improving efficacy?[2] Teclistamab was