

Although this finding is interesting, the clinical relevance is limited because predicting the ultimate severity of respiratory complications is impossible before glucocorticoid treatment.

Redlich et al. note that neonatal hypoglycemia has been associated with impaired neurologic outcome and that betamethasone should not be recommended until long-term follow-up has been conducted. Although betamethasone was associated with a higher rate of neonatal hypoglycemia than placebo, we also found that infants in the betamethasone group had fewer prolonged stays in special care nurseries (32.9% vs. 37.0%, $P=0.03$). Infants with hypoglycemia, regardless of the study group, had shorter median stays in special care nurseries, which suggests that the hypoglycemia resolved quickly (unpublished data). This is reassuring, since it is thought that adverse neurologic outcomes are associated with persistent, prolonged hypoglycemia.^{1,2} Additional analyses may characterize the occurrence of hypoglycemia in our trial.

Smith provides plausibility for an association between the use of betamethasone and impaired neurodevelopment and notes that in the ASTECS trial involving term cesarean deliveries, children in the glucocorticoid group were twice as likely to be assessed in the lowest quartile of achievement at school. This isolated finding was from a subjective assessment of school ability. There were no significant differences between groups in multiple other objective neurocognitive tests.³ In the 30-year follow-up of the Liggins and Howie trial, there were no significant between-group differences in neurodevelopmental outcomes among those randomized before 37 weeks of gestation.⁴

Likewise, no long-term effect of antenatal glucocorticoids on neurodevelopment has been found in meta-analyses of randomized trials.⁵ Nevertheless, we wholeheartedly agree on the need for further evaluation, and our long-term follow-up will provide additional data on the effect of betamethasone on neurodevelopment. We hypothesize that reductions in the risks of neonatal complications and the need for interventions probably outweigh any potential long-term adverse effects of betamethasone.

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Fruit Consumption and Cardiovascular Disease in China

TO THE EDITOR: In the article by Du et al. (April 7 issue)¹ on fresh fruit consumption and major cardiovascular disease in China, the epidemiologic findings of increasing mean body-mass index (BMI) and waist circumference with increasing daily fruit consumption were attributed to improved nutrition. Although the China Kadoorie Biobank Study is a prospective cohort study, the BMIs and waist circumferences reported were mean anthropometric values measured in a cross-sectional manner adjusted for age, sex, and geographic region, among various other appropriate

covariates. Such a conclusion is speculative and may be erroneously interpreted by readers to reflect visceral adiposity due to the deleterious effects of high fructose ingestion.² It might have been far more instructive if the researchers had measured BMI-adjusted waist circumference (WC_{BMI}) and then monitored its change longitudinally (ΔWC_{BMI} in centimeters per year), as described in two previous reports coauthored by Du, because WC_{BMI} is a marker of abdominal adiposity as well as a sensitive indicator of nutrient exposures and predictor of metabolic disease risk.^{3,4}

A negative association between fruit consumption and gains in WC_{BMI} has been shown.⁴

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TO THE EDITOR: The large prospective observational study by Du et al. showed that a higher level of fruit consumption, according to frequency and amount, was inversely and significantly associated with multiple baseline characteristics, such as systolic blood pressure and blood glucose level, and with incident cardiovascular outcomes. However, the reported effect of fresh fruit consumption on outcomes contradicts the almost total lack of interaction, in this study, of fresh fruit consumption with major baseline exposures, with regard to cardiovascular outcomes. One would expect that some of the major outcome associations with a broad nutritional exposure such as fresh fruit consumption — which by itself consists of numerous minerals and vitamins, for example, with potential health effects — would be modified by at least some of the known risk factors for cardiovascular outcomes, such as blood glucose level and systolic blood pressure. This fully independent effect of nutritional exposure on health outcomes may actually decrease its biologic plausibility¹ and could serve as yet another omen for the inherent complexity and caution needed when studying general nutritional effects on health.²⁻⁴

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TO THE EDITOR: In a prospective study involving a half million Chinese adults without antihypertensive treatment or prevalent cardiovascular disease, Du et al. reported that frequent consumption of fresh fruit was associated with a 25 to 40% lower risk of total and individual cardiovascular events than was nonconsumption. Dietary guidelines encourage fruit consumption.¹ Therefore, the reduced risk of cardiovascular disease may be due to the substitution of fresh fruit for some potentially unhealthy foods such as sugar-sweetened beverages and high-sodium foods (e.g., processed meat). An addition effect and a substitution effect could be explicitly compared by adding total energy intake in the multivariable model, which was not done in this study.

Du et al. addressed the potential confounder of socioeconomic status. However, the problem of confounding by other dietary factors (e.g., peanuts and whole grains) that may closely correlate with fruit consumption also merits consideration. In an analysis of two large population-based cohort studies involving Chinese adults, high consumption of peanuts was associated with a 24% lower risk of death from cardiovascular disease than was low consumption, with similar reductions in ischemic heart disease and stroke, after fruit and vegetable consumption was taken into account.²

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THE AUTHORS REPLY: As suggested by Leow, we further examined the association of fruit consumption with longitudinal changes in waist circumference adjusted for BMI (ΔWC_{BMI}) among the approximately 22,000 participants who took part in the second resurvey conducted from August 2013 through September 2014. This analysis showed that the positive association between fruit consumption and adiposity persisted: the ΔWC_{BMI} over a period of approximately 8 years was approximately 0.4 cm higher in daily consumers of fresh fruit than in those who never or rarely consumed fresh fruit (i.e., 0.05 cm per year). This finding appears to contradict the results of some Western studies¹ but concurs with previous findings in Chinese adults.^{2,3} The reasons for such conflicting results merit further investigation but were beyond the scope of our article.

Kopel appears to have misunderstood the subgroup results shown in Figure 3 of our article. Consistent associations across different subgroups indicated that none of the cardiovascular risk factors was an effect modifier. However, as shown in Figure S9 in the Supplementary Appendix (available with the full text of our article at NEJM.org), additionally adjusting for systolic blood pressure and blood glucose level attenuated the associations slightly (e.g., by approximately 12% for the association with hemorrhagic stroke), suggesting a potential mediating role of these two factors.

As to the comments by Chen and Qin: in China, fresh fruit is normally eaten as a snack rather than as a meal. Therefore, it is not likely that people would eat fruit to replace whole-grain foods. We have adjusted our analyses for meat and preserved vegetables, as a proxy marker of salt consumption. Not being able to adjust for total energy intake is a limitation of our study, but this should not invalidate our conclusions, because models including both total physical activity and BMI (two parts of the energy-balance equation) yielded identical results (Fig. S9 in our

Supplementary Appendix). We did not collect information on consumption of sugar-sweetened beverages at the baseline survey. However, at the 2013–2014 resurvey, only 6% of the participants consumed sugar-sweetened beverages on a weekly basis (top category), and the percentage varied slightly across five categories of fruit consumption (from 3.7% among those who never or rarely consumed fruit to 6.9% among daily consumers). This weak positive, instead of negative, correlation implies that the observed associations between fruit consumption and cardiovascular disease should not be due to the substitution of fresh fruit for sugar-sweetened beverages. As for peanut consumption, again we did not collect such data given that the population level of consumption in China is very low (i.e., an average of approximately 2 g per day in the studies conducted in Shanghai⁴). It is unlikely that such an unmeasured factor could explain our findings.⁵

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Radiation plus Chemotherapy in Low-Grade Glioma

TO THE EDITOR: Buckner et al. (April 7 issue)¹ report the first randomized trial (Radiation Therapy Oncology Group [RTOG] 9802) showing an overall survival benefit in adult patients with newly diagnosed low-grade glioma. A striking

difference in the median overall survival (5.5 years more) was observed between adjuvant chemotherapy (procarbazine, lomustine, and vincristine [PCV]) added to radiotherapy and radiotherapy alone. A comprehensive molecular characteriza-