quested. The sponsor policy related to data sharing was not taken into account. Some sponsors agree to share only selected studies. However, the purpose of the study was to evaluate the amount of available data, regardless of whether a trial was not listed because of company policy or for another reason. In addition, only 1 repository was evaluated.

Isabelle Boutron, MD, PhD
Agnes Dechartres, MD, PhD
Gabriel Baron, PhD
Jacques Li
Philippe Ravaud, MD, PhD

Author Affiliations: INSERM UMR 1153, Paris Descartes University, Paris, France (Boutron, Dechartres, Baron, Ravaud); Centre d'Épidémiologie Clinique, Hôpital Hôtel Dieu, Assistance Publique des Hôpitaux de Paris, Paris, France (Li).

Corresponding Author: Isabelle Boutron, MD, PhD, Centre d'Epidémiologie Clinique, Hôpital Hôtel Dieu, Aile A2 1er étage, 1, Place du parvis Notre Dame, 75181 Paris Cedex 4 (isabelle.boutron@htd.aphp.fr).

Author Contributions: Drs Boutron and Baron had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Boutron, Dechartres, Ravaud.
Acquisition, analysis, or interpretation of data: Boutron, Dechartres, Baron, Li.
Drafting of the manuscript: Boutron.
Critical revision of the manuscript for important intellectual content: Dechartres, Baron, Li, Ravaud.
Statistical analysis: Baron.
Obtained funding: Ravaud.
Administrative, technical, or material support: Li.
Study supervision: Ravaud.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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COMMENT & RESPONSE

Prenatal Vitamin D and Offspring Wheezing

To the Editor Dr Litonjua and colleagues reported the results of a randomized clinical trial investigating the effect of prenatal supplementation with vitamin D on asthma and wheezing in young offspring.[1] The study provides an example of the problems with so-called "statistical significance" and the interpretation of *P* values with reference to an arbitrary threshold. The authors estimated that high-dose vitamin D given in pregnancy was associated with a reduced risk of the coprimary outcome of recurrent wheeze (hazard ratio [HR], 0.8 [95% CI, 0.6-1.0]), with an associated *P* value of .051.

The conclusion of the article emphasized that this result "did not meet statistical significance" (the *P* value was >.05). The implication is that, had the *P* value been just .002 lower (ie, *P* = .049), the authors might have presented their final conclusion with a different emphasis, noting "statistical significance," and the trial results might have been interpreted more positively, with a conclusion that prenatal supplementation with vitamin D had a beneficial effect.

Yet the statistical meanings of both *P* = .051 and *P* = .049 are similar: if the null hypothesis were true (no real treatment effect), and the trial were repeated many times, a difference between the treatment groups at least as large as observed would be expected about once every 20 times due to chance variation alone.

The problems with arbitrarily dichotomizing results into statistically significant or nonsignificant have been noted for many years, and major journals now expect authors to present CIs and exact *P* values, offsetting some of the problems with this approach.[2-4] Litonjua and colleagues rightly pointed out that their study may have lacked power and that the CIs did not preclude a clinically important protective effect of supplementation. Despite this, the focus on a binary notion of statistical significance still persists, and we think that it colors the interpretation of results in an overly simplistic way. We suggest that such terminology be avoided, with *P* values interpreted as a continuous measure of strength of evidence against the null hypothesis.

With this approach, this trial might have been interpreted as providing some, but not strong, evidence of a protective effect of supplementation during pregnancy on recurrent wheeze in offspring, and the range of possible clinically relevant benefits might have been better emphasized in key parts of the article. This interpretation would be similar with *P* = .051 or *P* = .049.

Krishnan Bhaskaran, PhD
Liam Smeeth, PhD
Stephen Evans, MSc

Author Affiliations: Department of Noncommunicable Diseases Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom (Bhaskaran, Smeeth); Medical Statistics Department, London School of Hygiene and Tropical Medicine, London, United Kingdom (Evans).

Corresponding Author: Krishnan Bhaskaran, PhD, Department of Noncommunicable Diseases Epidemiology, London School of Hygiene and Tropical Medicine, Keppel St, Room 256, London, WC1E 7HT, United Kingdom (krishnan.bhaskaran@lshtm.ac.uk).

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1. Litonjua AA, Carey VJ, Laranjo N, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: the VDAART randomized clinical trial. *JAMA*. 2016;315(4):362-370.

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To the Editor A study of vitamin D supplementation in pregnancy found the incidence of asthma and recurrent wheeze in offspring at age 3 years was lower by 6.1% compared with placebo.[1] However, the 6.1% difference was not statistically significant and the trial was negative, but a reader would never know that reading the abstract.

The trial was designed to detect a 25% reduction in the incidence of asthma and recurrent wheeze in the first 3 years of life in the supplemented group, which is not mentioned in the abstract. The study concluded that it may have been underpowered. This was a negative trial. It appears to have been well done, the sample size was well thought out, and patients were adherent. Why then would the authors present these results as anything but negative and imply that more research is needed to examine this issue?

Dan Merenstein, MD
Frank D'Amico, PhD

Author Affiliations: Department of Family Medicine, Georgetown University Medical Center, Washington, DC (Merenstein); McAnulty College and Graduate School of Liberal Arts, Duquesne University, Pittsburgh, Pennsylvania (D'Amico)
.

Corresponding Author: Dan Merenstein, MD, Department of Family Medicine, Georgetown University Medical Center, 4000 Reservoir Rd NW, Bldg D 240, Washington, DC 20007 (djm23@georgetown.edu).

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1. Litonjua AA, Carey VJ, Laranjo N, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: the VDAART randomized clinical trial. *JAMA*. 2016;315(4):362-370.

In Reply Dr Bhaskaran and colleagues suggest that the interpretation of our study should be less dependent on the *P* value of .051, while Drs Merenstein and D'Amico suggest it should be more strict. We agree with Bhaskaran and colleagues that the 6.1% lower incidence of asthma and recurrent wheeze in the offspring with prenatal vitamin D supplementation may be better understood by considering the 95% CI.[1] The relative risk reduction was 20% (HR, 0.8) and the CI suggested that the effect of the intervention is likely to lie between a 40% reduction and no reduction (95% CI, 0.6-1.0). However, a misconception is that the true effect can lie with equal likelihood throughout the estimated CI, when in fact it lies with a greater likelihood around the 20% estimate than the extremes of the CI distribution.[1]

Merenstein and D'Amico are incorrect in that the abstract clearly states that the 6.1% absolute reduction was reported as not significant and the *P* value was presented, although the uncertainty in the reduction was also expressed. As Bhaskaran and colleagues suggest, the efficacy of an intervention should not be judged solely on the *P* value.[2] This misuse of the *P* value has long been the subject of warnings by statisticians[3] and is addressed by a statement by the American Statistical Association.[4]

We disagree with Merenstein and D'Amico in their suggestion that no further studies are needed on the issue of whether vitamin D supplementation in pregnancy can prevent asthma or recurrent wheezing in the child because the *P* value was not below an arbitrary threshold. We remind them that our trial was done on a cohort at high risk of asthma and on a multiracial cohort.

Thus, caution should be exercised in making sweeping statements about the effects of vitamin D. Because of these and other uncertainties discussed above and because of the growing realization that nutrient trials are different from drug trials, our study could have been designed in a better way. Nutrient trials are different from most other trials because the population is already exposed to the nutrient and individuals have circulating levels depending on the baseline intake of this nutrient, as Heaney[5] has pointed out. As seen in our trial, levels of vitamin D at entry were not the same in all participants, and the response to the dose of vitamin D may be different depending on the initial circulating levels. Thus, basal nutrient status must be measured. Other suggested guidelines are that the intervention must be large enough to change nutrient status; that the change in nutrient status must be measured and recorded; that the hypothesis tested must be that a change in nutrient status produces the effect of interest; and that conutrient status must also be optimized. Unfortunately, these guidelines were published after our trial started, and additional studies that account for the issues in these guidelines are needed before it can be truly known whether vitamin D supplementation taken during pregnancy can prevent asthma or recurrent wheeze in offspring.

Augusto A. Litonjua, MD, MPH
Scott T. Weiss, MD, MS

Author Affiliations: Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Corresponding Author: Augusto A. Litonjua, MD, MPH, Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115 (augusto.litonjua@channing.harvard.edu).

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Characteristics of Patients Dying With Cancer in Developed Countries

To the Editor A cross-national study[1] found differences in 7 developed nations in the place of death, health care utilization, and hospital expenditures for patients dying with cancer, a finding that might be surprising but corresponds with comparable studies.[2]