Letters

"did not meet statistical significance" (the \( P = .051 \)), with an associated lems with so-called "statistical significance" and the interpre-

Prenatal Vitamin D and Ossparent Wheezing

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

Prenatal Vitamin D and Ossparent 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


Corresponding Author: Isabelle Boutron, MD, PhD, Centre d’Épidémiologie 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.


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).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Smeeth reported receiving grants from Wellcome Trust, Medical Research Council, National Institute for Health Research, GlaxoSmithKline, and the European Union; personal fees from GlaxoSmithKline; being the unpaid chair of a trial steering committee for AstraZeneca; and being a trustee of the British Heart Foundation. No other disclosures were reported.


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. 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, Duquesine 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 (dmj23@georgetown.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Merenstein reported being an expert witness for General Mills, Proctor & Gamble, Bayer, and Nestle Healthcare on probiotic cases. No other disclosures were reported.

In Reply Dr Bhaskaran and colleagues suggest that the interpretation of our study should be less dependent on the P value. However, a misconception is that the true effect can lie with a greater likelihood around the 20% estimate than the extremes of the CI distribution.

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. This misuse of the P value has long been the subject of warnings and 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 concomitant 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).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Litonjua reported receiving royalties from UpToDate and Springer Humana Press. No other disclosures were reported.


Characteristics of Patients Dying With Cancer in Developed Countries

To the Editor A cross-national study 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.

Letters