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References
1. Ludwig DS, Aronne LJ, Astrup A, de Cabo R, Cantley LC, Friedman MI, Heymsfield SB, Johnson JD, King JC, Krauss RM, et al. The carbohydrate-insulin model: a physiological perspective on the obesity pandemic. Am J Clin Nutr 2021;114(6):1873–85.
2. Schwartz MW, Seeley RJ, Zelkser LM, Dzewonski A, Ravussin E, Redman LM, Leibel RL. Obesity pathogenesis: an Endocrine Society Scientific Statement. Endocr Rev 2017;38(4):267–96.
3. American Association for the Advancement of Science (AAAS). EurekAlert! Insulin regulates body fat independent of dietary carbohydrates. Science [Internet] Available from: https://www.eurekalert.org/news-releases/919847 (accessed 3 November 2021).
4. Ludwig DS. Second opinion: let’s focus more on what we eat, not how much. Medpage Today. 18 October 2021 [Internet]. Available from: https://www.medpagetoday.com/opinion/second-opinions/95104.
5. Toates FM, Booth DA. Control of food intake by energy supply. Nature 1974;251(5477):710–1.
6. Booth DA, Toates RM. No paradox in the control of energy intake. Nature 1978;275(5678):345.
7. Ebbeling CB, Feldman HA, Klein GL, Wong JMW, Bielak L, Steltz SK, Luoto PK, Wolfe RR, Wong WW, Ludwig DS. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. BMJ 2018;363:k4583.
8. Ludwig DS, Lakin PR, Wong WW, Ebbeling CB. Scientific discourse in the era of open science: a response to Hall et al. regarding the carbohydrate-insulin model. Int J Obes 2019;43(12):2355–60.
9. Ludwig DS, Greco KF, Ma C, Ebbeling CB. Testing the carbohydrate-insulin model of obesity in a 5-month feeding study: the perils of post-hoc participant exclusions. Eur J Clin Nutr 2020;74(7):1109–12.
10. Ludwig DS, Dickinson SL, Henschel B, Ebbeling CB, Allison DB. Do lower-carbohydrate diets increase total energy expenditure? An updated and reanalyzed meta-analysis of 29 controlled-feeding studies. J Nutr 2021;151(3):482–90.

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ASN guidelines on P values

Dear Editor:

The recently proposed guidelines by the American Society for Nutrition (ASN) journals on P values (1) correctly point out some of the problems with P values, but directly contradict the explicit and well-considered recommendation to abandon statistical significance testing by the American Statistical Association (2) and many other learned critiques by statisticians as reviewed by Hurlbert et al. (3) and Greenland et al. (4). It is not helpful for researchers to be confronted with conflicting recommendations. The ASN vision reflects a dominant but erroneous way of thinking and ignores the wealth of modern ideas on scientific inference. To justify significance testing, ASN guidelines (1) state that medical and nutritional research often requires making a binary choice (e.g., to declare a treatment effective or not, to recommend 1 set of nutritional recommendations or another, to further investigate or move on to another question). Even so, we would hope that a binary decision is not made only based on the presence or absence of an effect, but also and primarily on the magnitude of the effect. Dichotomizing P values simplifies that, after decades of progress in thinking about these issues, this misleading and simplified approach is being promoted by ASN.

The ASN guidelines (1) point out some well-known problems that have collectively been referred to as the 4 horsemen of the reproducibility apocalypse (5): publication bias, insufficient sample size, P-hacking, and HARKing (hypothesizing after results are known). They fail to address what is arguably the most important issue—namely, that most researchers interpret P values using flawed inferential reasoning (i.e., it is not the use, but the misuse of P values that is the main problem). They fail to consider a P value as a conditional probability (i.e., the probability of findings in the sample at least as extreme as observed, given that, in truth, there is no association in the sampled population). They are also looking “in
the wrong direction,” from hypothesized effect to data instead of the other way around.

To illustrate this point, consider a similar problem in clinical practice: a physician reports to a patient that the result of her diagnostic test was positive. When the patient asks whether the test result could be wrong, she would be poorly served with an answer that the test is highly specific (i.e., given the absence of disease, it is very unlikely that the test result is positive). The patient’s primary interest concerns the question: Given that my test result is positive, what is the probability of truly having the disease? This positive predictive value depends not only on specificity but also on sensitivity and the a priori probability of disease. A clinician weighs the evidence of a test result in view of her combined understanding of the biology of the disease, patient characteristics, and the pre-test probability of disease. That is why the interpretation is not left to the laboratory technician. Similarly, statistically significant results should be interpreted taking the prior expectation and plausibility of the null hypothesis into account. By intuition, people usually get this right. For example, consider a trial report with a statistically significant benefit obtained with a homeopathic, super-diluted remedy. People who do not believe in homeopathy are unlikely to believe the test results. Statistical testing is like interpreting a diagnostic test result by looking only at its specificity—that is, under the null hypothesis of no disease. Interpretation of statistical tests should also take into account the plausibility or likelihood of the alternative hypothesis, which depends on external or subjective knowledge. That is also why interpretation of study results should not be left to a simplistic statistical rule.

Statistical adjustment for multiple comparisons, as recommended by default in the ASN guidelines (1), results in an increased probability of false-negative results. It also undermines the interpretation of related endpoints (6). It is equivalent to a physician finding an abnormally low hemoglobin concentration in a patient but no longer judging it worthy of treatment because she also found iron deficiency. In their Figure 2, Sorkin et al. (1) show that the probability of at least 1 false-positive result occurring increases with the number of tests performed. This is true when test results are independent. Because, in practice, outcomes are typically related, the default should be to not adjust, and if adjustment is nonetheless done, it should be justified. Many other commentaries support this view, again summarized by Hurlbert et al. (3).

To assist in the interpretation of significance, the ASN guidelines (1) recommend that \( P \) values should be reported with a statement of the sample size, an estimate of the treatment effect, and its variability. This is 1 option, but it is very cumbersome and we do not believe that adding more statistical information would help the general reader in interpreting (non)significance. Why not demand instead that effects are reported with CIs? Contrary to what is stated in the AJCN guidelines (1), however, CIs do not give a range in which the true value of a parameter \( \theta \) is expected to lie. It is not Bayesian; a 95% CI does not mean that the probability that the true value of the parameter is in the interval is 95%. Instead, as conceived by Neyman (7), a 95% CI encompasses a range of hypothesized effect sizes that have a \( P \) value exceeding 0.05—that is, hypothesized effect sizes within this range would be compatible with the sample estimate \( x_0 \) if the \( P \) value would be set at 0.05. In mathematical notation: \( Pr(\theta | x_0) \neq Pr(x_0 | \theta) \). Some additional pitfalls in the interpretation of CIs are outlined by Greenland et al. (4).

In conclusion, we agree that \( P \) values should not be banned. But, they should generally not be dichotomized, they should never be reported as (non)significant, and they should not be used unless there are good reasons for doing so. Even better is to separate results into a point estimate and its corresponding 95% CI. Because all information about statistical precision is contained in CIs, it is not necessary to additionally report \( P \) values.

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References

1. Sorkin JD, Manary M, Smeets PAM, MacFarlane AJ, Astrup A, Priggeon RL, Hogans BB, Odle J, Davis TA, Tucker KL, et al. A guide for authors and readers of the American Society for Nutrition journals on the proper use of \( P \) values and strategies that promote transparency and improve research reproducibility. Am J Clin Nutr 2021;114:1–6.
2. Wasserstein RL, Schirm AL, Lazar NA. Moving to a world beyond “\( p < 0.05 \)” Am Stat 2019;73:1–19.
3. Hurlbert SH, Levine RA, Uts J. Coup de grâce for a tough old bull: “statistically significant” expires. Am Stat 2019;73(Suppl 1):352–7.
4. Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. Statistical tests, \( P \) values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol 2016;31(4):337–50.
5. Bishop D. Rein in the four horsemen of irreproducibility. Nature 2019;568(7753):435.
6. Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. Lancet North Am Ed 2005;365(9470):1591–5.
7. Neyman J. Outline of a theory of statistical estimation based on the classical theory of probability. Phil Trans Royal Soc London Ser A 1937;236:333–80.

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Reply to Verhoef et al.

Dear Editor:

We thank our colleagues, Verhoef et al., for their thoughtful reply (1) to our article, “A guide for authors and readers of the American Society for Nutrition Journals on the proper use of \( P \) values, and transparency, to improve research reproducibility” (2).

Our colleagues state that we “directly contradict the explicit and well-considered recommendation to abandon statistical significance testing by the American Statistical Association.” We do not. In the American Statistical Association (ASA) Statement on Statistical Significance and \( P \)-Values (3), the ASA does not state that \( P \) values should be banned but rather that they should be used in proper context.

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