Lowering the p-value threshold to alleviate information crisis in nutritional epidemiology – a possible temporary solution?

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Abstract

Nutritional epidemiology has often been criticized by its inconsistency of results, these that are daily broadcasted to the media due to the public interest in the topic. Effect sizes in nutritional epidemiology are often small and biases are present. The cut-off of statistically significant results in the field currently is by the norm the 5% threshold, that is, $p < 0.05$ equals to a positive finding. Recent evidence found that lowering this threshold makes less claims to hold true. This said, lowering the alpha level in nutritional epidemiology could reduce the scenario in the field characterized by high frequency of positive and probably implausible findings. Of course, this would require a culture shift towards encouragement of negative findings, already proposed in some fields of science.

Introduction

Did you know? You are what your mother eats. Breakfast cereal can be strongly associated with infant sex, and women producing male infants consume more breakfast cereal than those with female infants (1).

Nutritional epidemiology has often been criticized by its inconsistency and irreproducibility of its results and claims (2–5), these that are broadcasted daily to the media due to the public interest in the topic (3,6).

Individual nutrients such as alfa-tocopherol and vitamin D can increase or decrease the risk of mortality in observational studies, depending on what variable the analyzer is adjusting in its regression model (7). It is well know that reductionist approaches are not encourage anymore in the field (8,9), but still studies are conducted in a reductionist point of view.

Even harsh critics recognize that diet could play a whole in preventing disease, but the problem seems to be more on inconsistency and misinformation (3,6). Nutritional research, mainly nutritional epidemiology, with its inconsistency may adversely affect the public perception of science (3). Food can explain partly why populations get sick (10). Some highlight that the field needs a radical reform (3).

In a dichotomous scenario, results with low prior probability tend to be mostly false. This can be worsen if bias, flexibility of analysis, smaller effects and financial and non-financial conflicts of interest are present (11). Effect sizes in nutritional epidemiology are often small (3,4), even if dietary patterns approach have effects that are a little stronger (3), and there is a discussion about non-financial conflicts of interest and bias in the field (12). This is worsened due to the fact that many nutritional exposures are correlated with one another and with other exposures who might have tiny effects on outcomes. Formally speaking, confounding (5).

If effect sizes in nutrition are often small, how come in a meta-analysis all individual foods reveal statistically significant associations with mortality (13)? Cumulative biases

of different names and origins may be at play (2,12,14). In this sense, what is a statistically significant result anyway?

The p-value and statistical significance

More formally, a p-value measures the probability of observing a test statistic equal or more extreme than the one that was observed, given that a test hypothesis is true (usually the null model, that is, the null hypothesis), and if every other model assumption used to calculate it were correct. It will also depend on degrees of freedom ^a (15).

These other assumptions include that some sort of random process was employed (random sampling, etc.), that there are no uncontrolled sources of bias (confounding, programming errors, equipment defects, and that the test hypothesis (often the null hypothesis) is correct (16). Fisher himself emphasized the need of randomization for the validity of a test of significance (17). P-values are heavily influenced by violations of validity such as uncontrolled nonlinearity, confounding, measurement error, selection bias, P-hacking, or even fraud. Because almost all assumptions are uncertain in a given study, a small P value only signals that there may be a problem with at least 1 assumption, without saying which one (18). This is partly the case why p-values have proposals of corrections in observational research (19). Like the famous statistician George Box once said: “all models are wrong, but some of them are useful (20).

The P value can be viewed as a continuous measure of the compatibility between the data and the entire model used to compute it, ranging from 0 for complete incompatibility to 1 for perfect compatibility (15). More formally, a P value does not test only 1 hypothesis, it is a test of every assumption used to compute the test. A so-called null test is a test of a model comprising all assumptions used to compute the P value, including validity assumptions as well as the null hypothesis. But the key here is that one often assume that all of them are correct before calculating the statistic (18). This is the emphasis here: “you assume that all of them are correct before calculating the statistic. That’s why George Box said what he said. You assume some conditions and calculate the compatibility of the data against them.

^a Degrees of freedom (df) are determined from the sample size and must be calculated to obtain the p-value. Commonly, in statistical analysis the total df is equal to the sample size minus 1 ($N - 1$), and with every parameter estimated, a df is subtracted from the total. More formally, there are more than one way of describing degrees of freedom. One,

is the number of items in a system that are free to vary given a set of constraints. For example, if we know that the values 270, 269 and 271 give a mean value of 270, calculating a mean is a constraint because three numbers can no longer take any value, once the first two numbers have been defined, the third can only be one value given that the mean has been defined. More generally, if n is the number of observations and c is the number of constraints, then $df = n - c$. A second definition is that df are the number of additional measurements beyond what is strictly required to estimate a quantity of interest. If one wants to estimate the weight of a person, one measurement is required. But if three measurements are taken, then $df = 3 - 1 = 2$. A third definition can be that df are the number of observations minus the number of parameters, where a parameter is a value from the data such as the mean of a group or the slope of a line. If the mean of body weight of a person is the only parameter estimated, then $df = 3 - 1 = 2$ (21).

Too often, however, the P value is interpreted in a dichotomous way in which results are declared “statistically significant” if P falls on or below a cut-off (usually 0.05) and declared “nonsignificant” otherwise (15). This is not compatible with the Neyman-Pearson approach nor with the Fisherian approach (22,23).

In the Neyman-Pearson approach, we justify an alternative hypothesis based on an a priori effect size and compare the null hypothesis with an alternative hypothesis under the observed p -value that is computed under the analyzed data. Power calculations of sample size are performed to assess the probability of getting a statistically significant result in the sample if this effect is present in the population. In this sense, p -values can be a function of sample size and by increasing sample size enough it is guaranteed that the null hypothesis can be rejected even with very tiny effect sizes (22,23).

In fact, what we have today is a sort of a bad and misunderstood mix between the Neyman-Pearson approach and the Fisherian approach, who specified no a priori power calculation nor a specific test hypothesis. Fisher intent was to test whether a hypothesis should be nullified, not implying that this hypothesis postulates a null difference or null effect (22–24). This mix is called the null ritual (24).

Why a cut-off of 0.05?

That’s the whole point. No one seems to know exactly. Early suggestions seem to come from William Gosset on the t -distribution, but nor Fisher nor Neyman and Pearson stated as a rule that the cut-off should be 0.05. In fact, they suggested that α should be set to the researcher (25). Somehow, a little later Cohen stated already that to balance the type I and type II, assuming an α of 5%, a power of 80% (and a β of 20%) would be interesting (25). By the time of Fisher, Neyman and Pearson, statistical books were published with their suggestions providing cookbook-like recipes on how to do statistics instead of encouraging thinking and presenting both approaches and discuss the situations in which each might be more appropriate (24). Nowadays, despite only suggestions of the

first proposers, mostly MEDLINE abstracts contain a $p < 0.05$ (26). It became a convention and a ritual, eliminating a researchers' own judgment (24).

Recent discussions on lowering the cut-off of 0.05 have been discussed in different fields (27–30). The practice of rounding up p values to a “significance level” ($p < .05$, $p < .01$, or $p < .001$) is supported neither by Fisher nor by Neyman and Pearson (24).

Also, discussions arise if the alpha should not be set in an individual study rather than into a whole field in order to balance type I and type II errors, an approach perhaps more in agreement with the first who endeavor into frequentism (24,25). In this scenario, lowering alpha as a function of sample size was proposed, but also as a function of a priori probabilities of the null hypothesis vs. the alternative hypothesis being true. The alpha should be lowered as the probability of H_0 increases and this require a subjective judgement (25). In nutritional epidemiology, claims were already made by different authors that associations between individual food/food groups/nutrients have low prior probability (11,31).

When analyzing nutritional exposures in NHANES, Ioannidis found that ~50% of any tested nutrient association with any outcome emerge significant, replicated across different waves of the survey, passing through false discovery rate and statistical significance. His conclusion was that one out of two analysis shots within nutritional epidemiology will give you a statistically significant result (5).

Lowering the cut-off in nutritional epidemiology

Not entering in the discussion about whether statistical approach is better, such as likelihood ratios (32), bayes factor (33) or Bayesian analyses (34) and despite of the many limitations of null hypothesis significance testing in biomedical research (23), it is still a statistical paradigm that is widely used by researchers (26), including in the nutritional epidemiology field.

In a recent umbrella review of individual food associations and risk of cancer in 11 anatomical sites, it was estimated that only few single food/nutrient and cancer associations are supported by strong or highly suggestive meta-analytic evidence, and

future similar research are unlikely to change the evidence (31). The study showed a very different scenario outlined before by individual studies where $p < 0.05$ hold (2).

Associations were supported by strong evidence if all the following criteria were met: the meta-analysis included >1000 cancer cases, a threshold that provides 80% power for hazard ratios ≥ 1.20 and the random-effects model had a P value $\leq 10^{-6}$. More formally, in this scenario, only alcohol consumption was positively associated with risk of postmenopausal breast, colorectal, esophageal, head & neck and liver cancer; dairy products, milk, calcium and wholegrains were inversely associated with colorectal cancer risk and coffee consumption was inversely associated with risk of liver cancer and skin basal cell carcinoma. Effect sizes are not very large, but are very likely to be real and many 95% confidence intervals are tiny (31).

Lowering the cut-off to a lower threshold in the field of nutritional epidemiology could reduce the quantity of positive findings in the field. Findings could only be proven positive in meta-analytical estimates with high power (31). This could contribute positively to the current information crisis in the field outlined above in this piece.

Of course, this should be accompanied by a cultural shift towards an incentive to publish null findings (i.e., findings that would not reach the pre specified cut-off of statistical significance), and some culture suggestions were already suggested and can be somewhat expanded to the whole biomedical literature (35).

Even if the p-value is a function of the sample size and even tiny effects can be found with enough samples (23), some findings still persevere after very low thresholds (31). Evidence could be cumulatively analyzed and the Bayes Factor could be used to verify continuously if the null hypothesis remained more probable after increasing sample size, since this statistic can provide some evidence of absence (33), and the p-value is not a good statistic to measure a scenario more compatible with evidence of absence, where in very small powered scenarios (if the association is very tiny for example but likely exists) almost all p-values can be equally likely, a scenario almost compatible with one when the null hypothesis is true (33). Bayes Factor could also be used to determine the alpha level (25). Also, equivalence tests and one-sided tests could be performed continuously to analyze how small the effect is and reject the presence of a smallest effect size of interest

and if further research is needed on that specific association (36). In the beginning or in the middle of the research phase on that specific association where effect sizes are not well estimated, type M and type S errors might help if the researcher has a hint on what is probably the true effect for that particular scenario under a particular sample size (37). Again, one can use multiple statistical tools.

One may not forget the importance of analyzing confidence intervals and point estimates, that is, effect sizes, together with the p-values in the results of the study. P-values merge the magnitude of the result with its precision; hence, similar p-values can be obtained for different point estimates and their confidence intervals. The presentation of effect size along with its confidence interval is required because they provide the two most important pieces of statistical information: the magnitude estimate of an effect of interest and the precision of that estimate. The presentation of both metrics encourage meta-analytical thinking and uncertainty (38), exactly the kind of thinking this opinion piece defends. It is common in many books of basic epidemiology to teach to give more emphasis on effect sizes and confidence intervals rather than p-values only. But again, null hypothesis significance testing is widely used.

Nutritional epidemiology is a field much broader than reductionist cohorts or cross-sectional studies of associations between single nutrients/foods and outcomes of interest, including disease, that are published just for the sake of one more publication in the curriculum and these are the studies that compose the main problem. But many researchers in the field adhere to good practices emphasizing more effect sizes rather than p-values, so lowering the cut-off in a research culture that emphasizes uncertainty and null findings would make not so much of a difference perhaps.

Lastly, one topic that is interesting to discuss here is abandoning statistical significance (39). One has to think of consequences on doing that (40,41). First, the fact that everyone uses p-values in a merge of Neyman-Pearson and Fisherian approaches (40). Of course, this does not discourage at all one to perform other types of statistics such as Bayesian (41). Who really like and propose themselves to study statistics (whether a statistician or not) should study not only frequentism but also bayesianism, likelihoods, and so on. But again, reinstating, the current opinion piece here assumes that null hypothesis significance tests are the norm (40) and only proposes a temporary solution. Even if proposing an

overall threshold of alpha to a given field may not be what the early frequentists proposed (24,25), that is what could be temporally possible perhaps. Again, more focusing on effect sizes and confidence intervals should be the recommended approach.

Difficulty in conducting randomized clinical trials in nutrition

Whether one can validate an exposure as an intervention is questionable (5). In a reproducibility effort of highly cited clinical research, 5 out of 6 observational studies were further “contradicted” by randomized trials (42) and one of them was an observational study where exposure was dietary consumption of vitamin E (43) and the replication that contradicted it was an randomized clinical trial that had vitamin E in pills as intervention compared with placebo (44). A previous estimate in nutrition using multiple concordance criteria concluded that in 23 out of 34 associations the summary findings from meta-analyses of epidemiological studies and of randomized controlled trials were in the same direction according to point estimates alone (45). Another recent estimate say high concordance rates between randomized trials and observational studies of dietary intake, biomarkers and other topics (46).

Statistical methods used to control for confounding are being more discussed in observational research in general, and this could lead perhaps to improved concordance (47,48). Recently, other approaches are being brought to nutrition, such as g-estimation (49).

Randomized clinical trials offer lower risk of bias in the evidence based pyramid when compared to observational studies (50). However, they are difficult to conduct in nutrition (3). Long trials have struggled with some loss to follow up, specially diet studies (51).

Observational studies often differ from randomized trials. A discrepancy between the observational study Women’s Health Initiative and the randomized trial Nurses’ Health Study estimates, could be largely explained by differences in the distribution of time since menopause and length of follow-up (52). In sum, the Nurses’ Health Study found that hormone replacement therapy offered risk to women, while the cohort of the Women’s Health Initiative found that therapy offered protection (42,47). Despite of that, the Nurses’ Health Study continues to be on headlines sometimes (47).

Findings of observational studies are often still believed to be correct even after presenting different results from randomized trials (5). The concordance between observational studies and randomized clinical trials vary in the literature (42,53–56). Newer analysis such as propensity scores doesn't seem to improve concordance (48,56), questions remain open in some cases (47) but of course this will depend.

Even if the concordance between randomized trials and observational studies vary and can be high depending on the criteria of concordance, observational studies still seem to be believed even after lack of concordance (5,47) and in nutrition many claims from reductionist observational studies are still conducted and make the headlines of the media and the news (6).

Changing statistical dichotomy will not solve everything – but can help

Not all media hype is necessarily generated by statistically significant results. Other types of extrapolations can be present, such as different kinds of spins (57).

A recent news stated that “Eating a hot dog could take 36 minutes off your life” (58). This claim was based on a median of a single boxplot of an article that contained many analysis and a broader research question rather than simply studying hot dogs (59). This extrapolation was not under any statistical association.

Fraud or questionable research practices?

Lastly, it is important to note here that we are not discussing systematic fraud, that composes a tiny amount of the literature. Questionable research practices such as p-hacking are way more common (60). However, frauds do occur such as the study of chocolate and weight loss by Johannes Bohannon, who caught media attention, was later retracted and possibly was published in more than one scientific journal (61,62).

The field of nutrition as a whole has essential players and stakeholders interested in improving scientific rigor, reproducibility and the public trust in the field (63,64). One of

the goals of nutrition science that was highlighted between 2015 and 2020 was to improve scientific rigor (65).

Conclusions

Any association is currently plausible in nutritional epidemiology. This causes a misinformation of its findings to the public when the results of specially reductionist studies that are still frequent goes to the media.

Null hypothesis significance testing is the norm in many scientific disciplines, including nutritional epidemiology. The current cut-off for defining a finding statistically significant in the field, as usual, is 5%. Under the null hypothesis statistical testing paradigm, maintaining an equal criterion for different studies and fields may not be the best approach. Lowering the alpha level in nutritional epidemiology could reduce the scenario in the field characterized by high frequency of positive and probably implausible findings.

This would require a culture shift towards encouragement of negative findings, already proposed in some fields of science. Evidence could be continuously analyzed as studies get published to verify if the food/dietary pattern association require further investigation or if the effect is too marginal to be relevant.

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