The excellent article in the Journal by Boffetta et al. (1) on fruit and vegetable intake and cancer risk offers a nice example on why inferences based on P values are problematic in large studies that show associations of very small magnitude. The reported associations between high fruit and vegetable intake and cancer risk reached nominal levels of statistical significance \( P = .006 \) and \( P < .001 \), respectively, and the authors conclude that the study “supports the notion of a modest cancer preventive effect of high intake of fruits and vegetables” (1). The respective hazard ratios per 100 g/d intake of fruits and vegetables were 0.99 and 0.98, respectively, and 0.97 per 200 g/d intake of fruits and vegetables combined. The authors are commended for being cautious that residual confounding can affect such hazard ratios of very small magnitude (1). The main problem, however, is that for associations of very small magnitude, P values alone do not suffice to make inferences,
even if there is absolutely no residual confounding. The inferences depend critically on how strong the associations are expected to be based on previous results, biological reasoning, or practical considerations, that is, the associations that would be important from a clinical or public health perspective.

Table 1 shows simple calculations using Bayes factors to represent how the results of Boffetta et al. (1) modify one’s previous belief that an association exists between fruit and vegetable intake and cancer risk. Bayes factors are calculated using a lump-and-smear prior, as previously described (2). We estimate that despite their nominal statistical significance, the results of Boffetta et al. make it less likely that there is a protective association between fruit intake and cancer if the expected average hazard ratio for protective associations is less than 0.82 per 100 g/d. Moreover, regardless of assumptions, we estimate that the results of Boffetta et al. never make the presence of a protective association greater than eightfold more likely compared with previous beliefs. In Bayesian nomenclature, such results do not offer strong support for an association (3). The evidence for vegetable intake is slightly better, but still the best scenario makes the presence of a protective association 40-fold more likely compared with previous beliefs. This is nowhere close to decisive support, which is defined as making the presence of protective association greater than 100-fold more likely compared with previous beliefs (3). Moreover, modestly strong support is offered only if the prior considerations pertained to a minimal impact of vegetables on cancer risk (hazard ratio < 0.90 per 100 g/d). Early claims in the literature that were carefully reviewed by Willett (4) in an accompanying editorial suggested huge benefits. The results of Boffetta et al. (1) put to rest the extravagant claims from hundreds of case–control studies and small cohorts on fruit and vegetable intake and cancer (5).

This is a classic example of the Lindley’s (6) paradox that was described half a century ago but is becoming increasingly pertinent in current epidemiology. Despite statistically significant results, when the observed association has very small magnitude, the null hypothesis may become more likely relative to the alternative (2). Using P values to interpret these results creates misconceptions (7). Several statistically significant results from large studies in nutritional epidemiology and related fields represent small effect sizes and may fall in the same category.

Nominal statistical significance alone means very little in large studies. It is essential to report the expected effects for probed risk factors against which the new accumulated data will be interpreted. Ideally, this should be done up front before any analyses are performed, clarifying also whether the magnitude of the expected associations is informed by previous studies, theory, or practical considerations. This approach would help improve the interpretation of these valuable investigations.

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References

Notes
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Table 1. The impact of the results of Boffetta et al. (1) on the credibility of an association between fruit or vegetable intake and cancer risk

<table>
<thead>
<tr>
<th>Average value of the expected hazard ratio (per 100 g/d) under the alternative hypothesis for protective associations</th>
<th>After the observed results, a protective association between fruit intake and cancer risk becomes*</th>
<th>After the observed results, a protective association between vegetable intake and cancer risk becomes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.98</td>
<td>Eightfold more likely</td>
<td>40-fold more likely</td>
</tr>
<tr>
<td>0.95</td>
<td>Fourfold more likely</td>
<td>20-fold more likely</td>
</tr>
<tr>
<td>0.90</td>
<td>Twofold more likely</td>
<td>10-fold more likely</td>
</tr>
<tr>
<td>0.80</td>
<td>Slightly less likely</td>
<td>Fivefold more likely</td>
</tr>
<tr>
<td>0.70</td>
<td>Twofold less likely</td>
<td>Threefold more likely</td>
</tr>
<tr>
<td>0.50</td>
<td>Fourfold less likely</td>
<td>1.5-fold more likely</td>
</tr>
</tbody>
</table>

* Calculations using Bayes factors were performed as described in reference (2).