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Evaluation of Lowering the *P* Value Threshold for Statistical Significance From .05 to .005 in Previously Published Randomized Clinical Trials in Major Medical Journals

Lowering the threshold for statistical significance in medical research from a *P* value of .05 to .005 was recently proposed to reduce misinterpretation of study results.[1,2] *P* values less than .05 but greater than .005 would be reclassified as "suggestive." What effect this proposal would have on the medical literature is unclear. We evaluated primary end points in randomized clinical trials (RCTs) published in 3 major general medical journals with high impact factors to determine how the new threshold could affect the interpretation of previously published RCTs.

Table 1. Characteristics of Included Clinical Trials or End Points

Characteristics	No. (%) of Articles (N=203)
Journal	
JAMA	69 (34.0)
Lancet	31 (15.3)
NEJM	103 (50.7)
Intervention	
Drug	124 (61.1)
Procedure	41 (20.2)
Device	9 (4.4)
Vaccine	2 (1.0)
Other	21 (10.3)
Mixed	6 (3.0)
Funding source	
Industry	76 (37.4)
Public	81 (39.9)
Private	6 (3.0)
Hospital	17 (8.4)
Mixed (no industry)	11 (5.4)
Mixed (with industry)	10 (4.9)
Not mentioned	2 (1.0)
No. of trial centers	
Multicenter	181 (89.2)
Single center	22 (10.8)
Location	
Multinational	105 (51.7)
Single country	98 (48.3)
Type of end point, No.	272
Mortality	27 (9.9)
Other	245 (90.1)
Sample size, median (IQR)	565 (290-1215)

Abbreviations: IQR, interquartile range; *NEJM*, *New England Journal of Medicine*.

Methods | We searched PubMed from January 1, 2017, to December 31, 2017, for phase 3 RCTs published in *JAMA*, *Lancet*, and *New England Journal of Medicine* (*NEJM*). We excluded single-group trials, pooled analyses, RCTs without *P* values, and RCTs that used Bayesian or noninferiority analyses. Two authors (C. W., J. S.) screened all trials.

We extracted data for primary end points because RCTs are most often powered for these end points. The following data were extracted from each trial: *P* values for primary end points (excluding subgroups), study title, journal name, funding source, sample size, type of intervention, whether the end point was mortality, whether the trial was multicentered, and whether the trial was multinational. Data were extracted blinded and in duplicate. Discrepancies were resolved by consensus.

We first determined the proportion of end points that would maintain statistical significance with a threshold of *P* less than .005 and that would be reclassified as suggestive

Table 2. Analysis of Trial Characteristics and Reporting a *P* Value Less Than .005[a]

Covariables	No. (%) of Articles (N=203)		Odds Ratio (95% CI)	
	Total	With *P* Value <.005	Unadjusted	Adjusted
Journal				
JAMA	69 (33.9)	21 (30.4)	1 [Reference]	1 [Reference]
NEJM	103 (50.7)	57 (55.3)	2.83 (1.49-5.39)	1.79 (0.73-4.37)
Lancet	31 (15.3)	19 (61.3)	3.62 (1.49-8.78)	2.06 (0.65-6.50)
Funding source[b]				
Nonindustry	115 (56.6)	38 (33.0)	1 [Reference]	1 [Reference]
Industry	86 (43.4)	59 (68.6)	4.66 (2.55-8.51)	7.87 (3.14-19.71)
No. of trial centers				
Multicenter	181 (89.2)	86 (47.5)	1 [Reference]	1 [Reference]
Single center	22 (10.8)	11 (50.0)	1.10 (0.46-2.68)	1.89 (0.60-5.92)
Location				
Multinational	105 (51.7)	56 (53.3)	1 [Reference]	1 [Reference]
Single country	98 (48.3)	41 (41.8)	1.59 (0.91-2.77)	1.62 (0.61-4.29)
Type of end point				
Mortality[c]	26 (12.8)	8 (30.8)	1 [Reference]	1 [Reference]
Other	177 (87.2)	89 (50.3)	2.28 (0.94-5.50)	2.56 (0.94-6.98)
Type of intervention[d]				
Procedure	41 (20.2)	12 (29.3)	1 [Reference]	1 [Reference]
Drug	124 (61.1)	64 (51.6)	2.58 (1.21-5.51)	1.11 (0.43-2.88)
Other	21 (10.3)	13 (61.9)	3.93 (1.30-11.90)	3.69 (0.94-14.49)
Sample size[e]			1.00 (0.99-1.00)	

Abbreviation: *NEJM*, *New England Journal of Medicine*.

[a] Logistic regression model adjusted for journal, funding source, number of trial centers, location, type of end point, type of intervention, and sample size.

[b] Two articles did not mention funding source.

[c] Refers to trials with at least 1 mortality end point.

[d] Excludes vaccine, mixed, and device interventions due to low event rates.

[e] Based on a continuous measure.

(ie, *P* values >.005 but <.05). Second, we investigated trial characteristics associated with reporting at least 1 primary end point with a *P* value less than .005 using a logistic regression model adjusting for all extracted trial characteristics. We used Google Forms for data extraction and STATA version 13.1 (StataCorp) for the data analysis.

Results | Of 290 articles retrieved, 203 were included. The 87 excluded were mostly phase 1 or 2 trials (n = 26), noninferiority or Bayesian analyses (n = 26), or pooled analyses (n = 11) or did not report *P* values (n = 10). Characteristics of included RCTs are outlined in **Table 1**.

We identified 272 primary end points from 203 trials: 174 end points had a *P* value less than .05 and 98 had a *P* value greater than .05. Overall, 70.7% (123 of 174) of statistically significant primary end points were less than .005, whereas 29.3% (51 of 174) were between .005 and .05 and would be reclassified as suggestive. Of these 272 total *P* values, 53.5% (76 of 142) in *NEJM*, 47.7% (21 of 44) in *Lancet*, and 30.2% (26 of 86) in *JAMA* were less than .005.

We next analyzed the 203 trials to determine which trial characteristics were associated with reporting at least 1 *P* value less than .005. Before adjusting for covariates, industry funding, drug and "other" (eg, nonpharmacological) interventions, and trials published in *NEJM* and *Lancet* were associated with primary end points that met the new threshold for significance of *P* less than .005. Sample size, multicenter trials, multinational trials, and mortality end points were not related to maintaining statistical significance. After adjusting for covariates, only trials with industry funding (n = 86) were more likely to report primary end points that would maintain statistical significance (59 of 86 articles [68.6%] with industry funding vs 38 of 115 [33.0%] without industry funding; adjusted odds ratio, 7.87; 95% CI, 3.14-19.71) (**Table 2**).

Discussion | Of statistically significant primary end points in RCTs published in 2017 in 3 major general medical journals with high impact factors, 70.7% would maintain their statistical significance with a *P* value threshold of less than .005. A .005 threshold for significance may address the shortcomings of *P* values, such as spurious false-positive results,[3] *P*-hacking (when researchers analyze data multiple ways until a significant effect is found),[4] and underpowered RCTs.[5] Furthermore, a .005 threshold may encourage a reliance on effect sizes rather than *P* values. A comparison between interventional and observational studies is warranted to evaluate the study type most affected by the proposed significance threshold change.

This study included only 3 high impact factor general medical journals over a 1 year period; thus, the results may not be generalizable.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
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COMMENT & RESPONSE

Medications With Depression as an Adverse Effect

To the Editor In a cross-sectional survey study, Dr Qato and colleagues[1] found that the use of prescription medications with depression as a potential adverse effect was common. However, the authors did not take into account that most of the drugs described are used to treat conditions already linked to an increased risk of depressive symptoms. Although they investigated the relationship between hypertension and depression, they did not account for the association of depressive symptoms with pain (and subsequent use of pain killers), gastroesophageal reflux disorder (and subsequent use of gastrointestinal agents), or atopic disorders, such as asthma or allergic rhinitis (and the use of montelukast and antihistamines). Interestingly, these conditions are related to persistent low-grade inflammation,[2] an important factor associated with depression, which could not be accounted for in the study.

The increase in prescription of such drugs follows the increased prevalence and survival of people with chronic conditions in the United States.[3] In Table 1 in the article, the patients taking drugs associated with depression included more women, older people, widowed or divorced people, and people with higher levels of unemployment and obesity, factors also associated with an increased risk of depression in nonmedicated populations. This group also had more comorbidities, which may have additive inflammatory and psychological effects. People with more than 1 medical comorbidity tend to have more depressive symptoms, increasing with the number of disorders, without the etiology being related to adverse drug reactions.[4]

The study did not investigate the converse—drugs that can be associated with a reduction in risk of depressive symptoms. Anti-inflammatory drugs or drugs for other conditions that exhibit anti-inflammatory properties, such as statins, acetylsalicylic acid, some hypoglycemic agents, drugs that act in the renin-angiotensin-aldosterone system, and immunomodulators, may have beneficial effects on mood, at least in subgroups of people.[5]

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To the Editor Dr Qato and colleagues[1] studied common prescription drugs associated with depression as an adverse effect. The authors controlled for the number of self-reported chronic conditions and performed sensitivity analysis of patients with hypertension. However, one factor that may play a role in the results that the authors did not discuss is the severity of illness of the patients.

More severe forms of chronic illnesses, such as hypertension, can be associated with higher levels of depressive symptoms.[2] Could it be that more severe forms of disease are associated with the use of drugs that have depression listed as an adverse effect? Clinicians may be less likely to prescribe certain drugs unless a condition is severe and is uncontrolled with other, more benign medications. For instance, in primary care in the United Kingdom, most patients with hypertension are not prescribed β-blockers unless their hypertension is uncontrolled with other agents. While the sensitivity analysis of patients with only hypertension showed a statistically significant difference between those taking