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Trends of Publication of Negative Trials Over Time

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Studies with negative results are less likely to be published than others, potentially leading to publication bias. Introduced in 2000, trial registration could have participated in decreasing the proportion of unpublished studies. We assessed the proportion of negative randomized controlled trials (RCT) over the last 20 years. We searched Medline for RCT published in 2000, 2005, 2010, 2015, and 2020 in the British Medical Journal, the Journal of the American Medical Association, the Lancet, and the New England Journal of Medicine. The primary endpoint was the proportion of negative (final comparison on the primary study-endpoint without statistical significance or favoring the control arm) studies published in 2000 and 2020. Factors independently associated with the publication of negative studies were identified using multivariable analysis. A total of 1,542 studies were included. The proportion of negative RCT significantly increased between 2000 and 2020 (from 27.6% to 37.4%; $P = 0.01$), however, the trend over time was not significant ($P = 0.203$). In multivariable analysis, the following factors were associated with a higher proportion of published negative studies: superiority ($P < 0.001$), two-group trials ($P < 0.001$), number of patients ≥510 ($P < 0.001$), cardiology trials ($P = 0.003$), emergency/critical care trials ($P < 0.001$), obstetrics trials ($P = 0.032$), surgery trials ($P = 0.006$), pneumology trials ($P = 0.029$). Exclusive industry funding was associated with a lower proportion of published negative studies ($P < 0.001$). The proportion of published negative studies in 2020 was higher only when compared to 2000. During the two decades, no trend was noticeable. There is no clear relationship between trial registration and the publication of negative results over time.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Studies with negative results are less likely to be published than others, potentially leading to publication bias. Introduced in 2000, trial registration could have participated to decreasing the proportion of unpublished studies.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We assessed the evolution with time of the reporting of negative randomized controlled trials in high-impact general medical journals since the initiation of trial registration.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The proportion of published negative studies in 2020 was higher only when compared to 2000. However, during the two decades, no trend was noticeable. It therefore remains unclear whether there is a relationship between trial registration and the publication of negative results over time.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our study gives reference values for future research on the clinical trial landscape and is important in the fields of evidence-based medicine.

In 1980, a trial testing the efficacy of lorcainide (a class Ic antiarrhythmic agent) in patients with acute myocardial infarction, found more deaths in the treated group than in the placebo group. The development of lorcainide was stopped, but the results of this study were not published.[1] A few years later, increased mortality was observed in the Cardiac Arrhythmia Suppression Trial (CAST) I[2] and CAST II[3] trials in patients with acute myocardial infarction receiving encainide, flecainide or moricisine (also class Ic antiarrhythmic agents). This historical example highlights the importance of reporting the results of all clinical trials, even those that

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do not show expected results. Publication bias arises when studies are published or not, depending on their results.[4,5] Studies reporting positive/statistically significant results are more likely to be published leading to a publication bias that overestimates treatment effects and distorts the body of evidence available for clinical decision-making.[6,7] Consequently, literature contains a preponderance of "positive" trials relative to those that are unpublished.[8] Solutions have been proposed to reduce publication bias such as trial registration or electronic publication.[9] In 1997, the Food and Drug Administration Modernization Act mandated a registry of both federally and privately funded clinical trials[10] and a public web-based registry was created in 2000, on behalf of the National Library of Medicine.[11] Although Clinicaltrials.gov represents the most widely used web-based registry,[12] other trial registries are publicly available, such as the International Standard Randomized Controlled Trial Number registry, or the European Union clinical trial registry. In 2005, the International Committee of Medical Journal Editors required trial registration on a publicly available database as a condition of publication.[13] This was justified by the necessity to reduce publication bias and, therefore, to facilitate the publication of negative results. Additionally, in 2015, the World Health Organization (WHO) published a new statement on the public disclosure of clinical trial results.[14] Whether the efficacy of these measures led to an increase in published negative trials over time remains to be assessed. Our primary objective was to assess the evolution with time of the reporting of negative randomized controlled trials (RCT) in high-impact general medical journals since the initiation of the Clinicaltrials.gov registry. Our secondary objective was to assess the profile of negative studies as compared with positive ones.

METHODS

Search strategy

We searched in Medline for all RCT published in 2000, 2005, 2010, 2015, and 2020, in four high-impact general medical journals: the *British Medical Journal* (BMJ), the *Journal of the American Medical Association* (JAMA), the *Lancet*, and the *New England Journal of Medicine* (NEJM). The following algorithm was used: ("JAMA"[Journal] OR "The New England journal of medicine"[Journal] OR "Lancet"[Journal] OR "BMJ"[Journal]) AND ("randomized controlled trial"[Publication Type]).

A data extraction sheet based on the Cochrane Handbook for Systematic Reviews of Interventions guidelines[9] was used. Data were extracted by teams of two independent reviewers (see authors contributions), and disagreements were resolved by a validation committee composed of five reviewers (B.L., C.Pa., J.-S.A., C.Lo., P.C.). For each RCT included, the following information was collected: (i) year of publication, (ii) medical specialty according to a 16-class classification, (iii) registration in a clinical trial registry, (iv) number of study arms, (v) number of patients randomized, (vi) funding (exclusive industry funding or not), (vii) study design (superiority, non-inferiority/equivalence trial), (viii) type of intervention (drug, medical device, therapeutic strategy including surgical procedures, or association of several types of interventions), (ix) type of comparator classified as placebo/no treatment or active treatment (studies with two or more control arms were considered as placebo-controlled if placebo was given in at least one arm), and (x) result on the primary outcome (i.e., statistically significant or not as defined by the original trial authors, and generally with *P*-value >5%).

Data analysis

The primary endpoint was the proportion of negative studies published in 2000 and 2020 (i.e., 5 years before and 10 years after the International Committee of Medical Journal Editors required clinical trial registration as a condition of publication). Superiority trials were considered negative when the result on the primary endpoint did not reach statistical

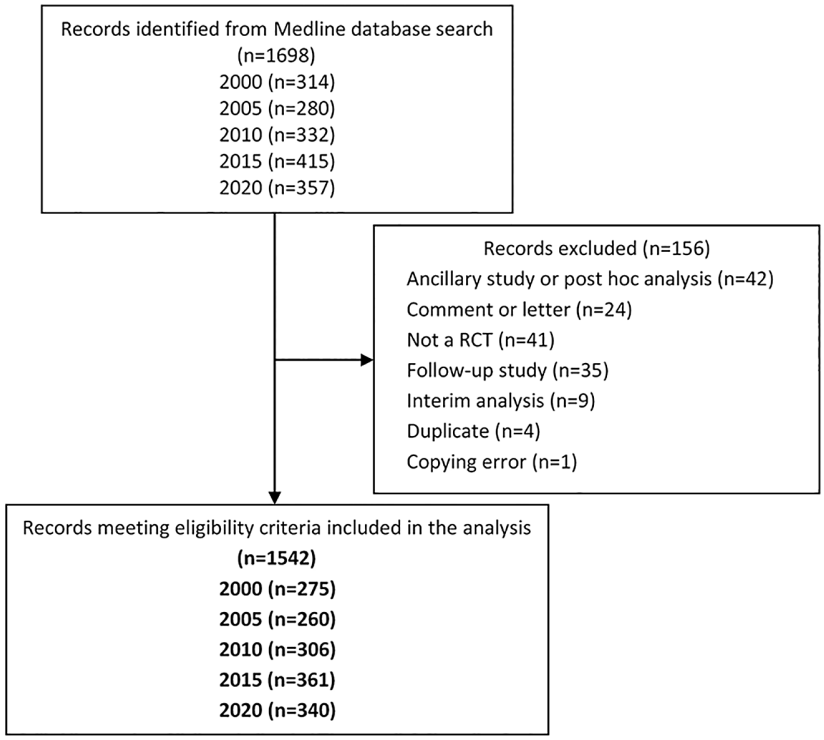

Figure 1 Flow chart.

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Table 1 Characteristics of included studies

	Year of publication					
	2000	2005	2010	2015	2020	All
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
	n = 275	*n* = 260	*n* = 306	*n* = 361	*n* = 340	*n* = 1,542
Results						
Positive RCT	199 (72.4)	157 (60.4)	210 (68.6)	250 (69.3)	213 (62.6)	1,029 (66.7)
Negative RCT	76 (27.6)	103 (39.6)	96 (31.4)	111 (30.7)	127 (37.4)	513 (33.3)
Journal						
The British Medical Journal	42 (15.3)	51 (19.6)	52 (17.0)	28 (7.8)	20 (5.9)	193 (12.5)
The Journal of the American Medical Association	56 (20.4)	52 (20.0)	47 (15.4)	63 (17.5)	75 (22.1)	293 (19.0)
The Lancet	104 (37.8)	69 (26.5)	86 (28.1)	135 (37.4)	86 (25.3)	480 (31.2)
The New England Journal of Medicine	73 (26.5)	88 (33.8)	121 (39.5)	135 (37.4)	159 (46.8)	576 (37.3)
Registration						
No	275 (100.0)	218 (83.8)	1 (0.3)	2 (0.6)	0 (0)	497 (32.2)
Yes	0 (0)	42 (16.2)	305 (99.7)	359 (99.4)	340 (100)	1,045 (67.8)
Study design						
Superiority trial	257 (93.5)	235 (90.4)	274 (89.5)	306 (84.8)	301 (88.5)	1,373 (89.0)
Equivalence or non-inferiority	18 (6.5)	25 (9.6)	32 (10.5)	55 (15.2)	39 (11.5)	169 (11.0)
Number of arms						
One or more than two	73 (26.5)	58 (22.3)	68 (22.2)	90 (24.9)	63 (18.5)	352 (22.8)
Two	202 (73.5)	202 (77.7)	238 (77.8)	271 (75.1)	277 (81.5)	1,190 (77.2)
Type of comparator						
Placebo/No treatment	120 (43.6)	92 (35.4)	105 (34.3)	119 (33.0)	151 (44.4)	587 (38.1)
Active treatment	155 (56.4)	168 (64.6)	201 (65.7)	242 (67.0)	189 (55.6)	955 (61.9)
Type of intervention						
Drug	150 (54.5)	133 (51.2)	164 (53.6)	207 (57.3)	226 (66.5)	880 (57.0)
Medical device	11 (4.0)	16 (6.2)	16 (5.2)	11 (3.0)	18 (5.3)	72 (4.7)
Therapeutic strategy	98 (35.6)	100 (38.5)	117 (38.2)	131 (36.3)	93 (27.4)	539 (35.0)
Association	16 (5.8)	11 (4.2)	9 (2.9)	12 (3.3)	3 (0.9)	51 (3.3)
Funding						
Partial industry funding or academic funding	221 (80.4)	209 (80.4)	223 (72.9)	247 (68.6)	232 (68.2)	1,132 (73.5)
Exclusive industry funding	54 (19.6)	51 (19.6)	83 (27.1)	113 (31.4)	108 (31.8)	409 (26.5)
Number of patients randomized						
<510	174 (63.3)	128 (49.2)	136 (44.4)	165 (45.7)	167 (49.1)	770 (49.9)
≥510	101 (36.7)	132 (50.8)	170 (55.6)	196 (54.3)	173 (50.9)	772 (50.1)

Data are expressed as number (corresponding percentage).

significance for superiority or favored the control arm. Non-inferiority/equivalence trials were considered negative if they did not meet the statistical requirement for non-inferiority/equivalence. Preliminary investigations based on the first 70 published RCT in 2000 suggested an expected proportion of negative studies of 30%. We hypothesized an absolute increase of this proportion of 15% between 2000 and 2020. Under these assumptions, a sample size of at least 268 studies each year was necessary, using a two-group Chi-square test with a 0.05 two-sided significance level and a power of 95%. In order to consider non-eligible studies (ancillary study or *post hoc* analysis, non-randomized study, comment, follow-up study, interim analysis), all studies identified by our Medline search were screened by the teams of reviewers. To assess the evolution of the proportion of negative studies published over time, the same rule was applied for 2005, 2010, and 2015. Evolution over time was investigated using a Cochran-Armitage trend test.

As no log linearity was respected for the number of subjects, for easier results interpretation we chose to dichotomize at the median of the distribution. Comparisons between negative and positive studies, irrespective of the year of publication, were carried-out using chi-square tests. To further assess the profile of negative studies, multivariable analysis was conducted using a logistic regression model. In this analysis, no *a priori* independent predictive variables were considered, and a single multivariable

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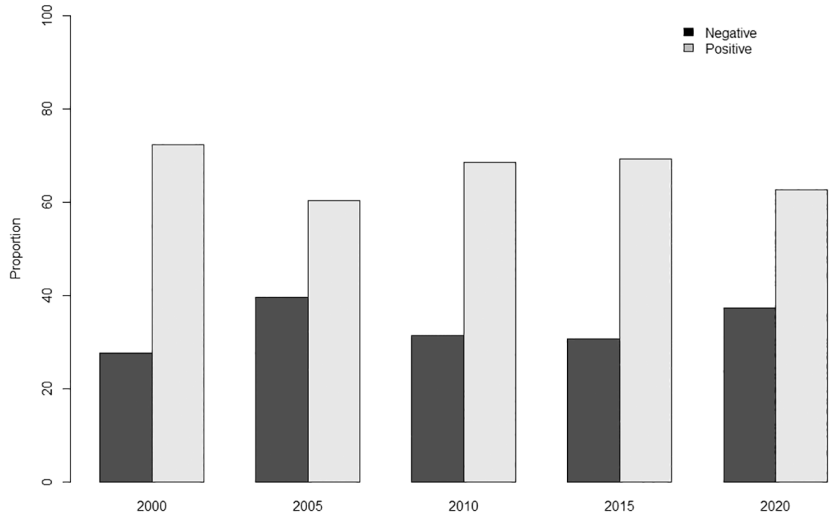

Figure 2 Proportion of negative studies over time.

model with all variables was performed. As in 2020 many negative trials were published on SARS-CoV-2 infection, we also performed a sensitivity analysis on the primary endpoint, excluding SARS-CoV-2 trials. For all analyses, a two-sided *P*-value <0.05 was considered significant. All analyses were performed using R software version 4.3.2 (2023-10-31).

RESULTS

A flow chart detailing the study selection process is given in **Figure 1**. Searches in Medline provided a total of 1,698 citations that were classified by date of publication, and 156 non-eligible studies were excluded. The remaining 1,542 studies were included in the analysis.

The characteristics of selected studies are presented in **Table 1**. As expected, the proportion of trial registration increased over time to achieve 100% in 2020. The majority of published studies were two-group superiority trials, that compared an experimental treatment to an active comparator, and around two third of them were drug intervention studies.

Regarding the primary outcome, a significant increase in published RCT with negative results was observed between 2000 and 2020 (from 27.6% to 37.4%; $P = 0.01$). When excluding SARS-CoV-2 trials, the proportion of negative studies was 35.8% in 2020 and did not change the statistical significance. When considering all studied years, there was no significant increase in the proportion of negative studies (*P*-value for trend, $P = 0.203$, **Figure 2**).

Comparisons between negative and positive studies, irrespective of the year of publication, are presented in **Table 2**.

Univariate analysis identified 12 factors significantly associated with a higher proportion of published negative studies. The proportion of negative studies was significantly lower in the N Engl J Med as compared with the JAMA or the BMJ ($P < 0.001$). Negative studies were more frequent in superiority trials ($P < 0.001$), comparing 2 groups ($P < 0.001$), with a sample size ≥510 ($P < 0.001$), and in the fields of cardiology/vascular disease ($P = 0.008$), emergency medicine/critical ($P < 0.001$), obstetrics/gynecology ($P = 0.010$), and surgery ($P = 0.033$). Negative trials were significantly less frequent in exclusive industry funding studies ($P < 0.001$), and in the fields of endocrinology/nutrition ($P = 0.003$), oncology/hematology ($P < 0.001$), and immunology/vaccinology/allergology ($P = 0.029$). The type of intervention and the type of comparator were similar in positive and negative trials ($P = 0.429$ and $P = 0.715$, respectively). However, exclusive industry-sponsored studies used significantly more inactive comparator as compared to other funded studies (55.5% vs. 31.8%, $P < 0.001$). The proportion of published negative studies did not significantly differ with the registration status ($P = 0.699$).

Multivariable analysis identified 10 factors associated with a higher proportion of negative studies: the JAMA and the BMJ compared to the NEJM (respectively, OR = 1.77, 95% CI [1.27 to 2.47] $P = 0.001$, and OR = 1.71, 95% CI [1.15 to 2.55], $P = 0.008$), superiority (OR = 3.90, 95% CI [2.49 to 6.29], $P < 0.001$), two-group trials (OR = 1.70, 95% CI [1.27 to 2.31], $P < 0.001$), number of patients ≥510 (OR = 2.18, 95% CI [1.71 to 2.78], $P < 0.001$), cardiology trials (OR = 2.53, 95% CI [1.38 to 4.77], $P = 0.003$), emergency/critical care trials (OR = 5.53, 95% CI [2.55 to 12.43], $P < 0.001$), obstetrics trials (OR = 2.22, 95% CI [1.08 to 4.66], $P = 0.032$), surgery trials (OR = 2.70, 95% CI [1.35 to 5.51], $P = 0.006$), pneumology trials (OR = 2.48, 95% CI [1.10 to 5.66], $P = 0.029$). Exclusive industry funding was associated with a lower proportion of published negative studies (OR = 0.31, 95% CI [0.22 to 0.43], $P < 0.001$).

DISCUSSION

Our study shows that the proportion of published negative trials increased between 2000 and 2020 in high-impact medical journals and that negative studies are more likely to be large, superiority trials, and comparing two groups. However, given that the tendency of publication of negative studies over time was not significant, our findings do not fully support the idea of a reduction of publication bias since 2000 in high-impact journals.

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Table 2 Comparisons between negative and positive studies

	Trials characteristics					
	Positive	Negative	Univariable OR [95% Confidence limits]	*P*	Multivariable OR [95% Confidence limits]	*P*
	n = 1,029	*n* = 513				
Journal						
The New England Journal of Medicine	414 (71.9)	162 (28.1)	–		–	
The Journal of the American Medical Association	169 (57.7)	124 (42.3)	1.88 [1.40; 2.52]	<0.001	1.77 [1.27; 2.47]	0.001
The British Medical Journal	118 (61.1)	75 (38.9)	1.62 [1.15; 2.28]	0.0054	1.71 [1.15; 2.55]	0.008
The Lancet	328 (68.3)	152 (31.7)	1.18 [0.91; 1.54]	0.210	1.25 [0.93; 1.67]	0.135
Registration						
No	335 (67.4)	162 (32.6)	–		–	
Yes	694 (66.4)	351 (33.6)	1.05 [0.83; 1.31]	0.699	1.13 [0.88; 1.46]	0.354
Study design						
Equivalence or non-inferiority	142 (84.0)	27 (16.0)				
Superiority trial	887 (64.6)	486 (35.4)	2.88 [1.91; 4.49]	<0.001	3.90 [2.49; 6.29]	<0.001
Number of arms						
One or more than two	266 (75.6)	86 (24.4)				
Two	763 (64.1)	427 (35.9)	1.73 [1.33; 2.28]	<0.001	1.70 [1.27; 2.31]	<0.001
Type of comparator						
Active treatment	634 (66.4)	321 (33.6)				
Placebo/No treatment	395 (67.3)	192 (32.7)	0.96 [0.77; 1.19]	0.715	0.87 [0.65; 1.16]	0.357
Type of intervention						
Association	33 (64.7%)	18 (35.3%)				
Drug	602 (68.4)	278 (31.6)	0.85 [0.48; 1.56]	0.581	0.97 [0.51; 1.89]	0.934
Medical device	48 (66.7)	24 (33.3)	0.92 [0.43; 1.96]	0.821	0.66 [0.29; 1.51]	0.322
Therapeutic strategy	346 (64.2)	193 (35.8)	1.02 [0.57; 1.9]	0.942	0.61 [0.32; 1.21]	0.148
Funding						
Partial industry funding or academic funding	690 (61.0)	442 (39.0)				
Exclusive industry funding	338 (82.6)	71 (17.4)	0.33 [0.25; 0.43]	<0.001	0.31 [0.22; 0.43]	<0.001
Number of patients randomized						
<510	565 (73.4)	205 (26.6)				
≥510	464 (60.1)	308 (39.9)	1.83 [1.48; 2.27]	<0.001	2.18 [1.71; 2.78]	<0.001
Medical specialty[a]						
Cardiology/Vascular disease	157 (59.7)	106 (40.3)	1.45 [1.10; 1.90]	0.008	2.53 [1.38; 4.77]	0.003
Emergency Medicine/Critical care	22 (36.7)	38 (63.3)	3.66 [2.16; 6.35]	<0.001	5.53 [2.55; 12.43]	<0.001
Obstetrics/Gynecology	39 (52.7)	35 (47.3)	1.86 [1.16; 2.97]	0.010	2.22 [1.08; 4.66]	0.032
Surgery	52 (56.5)	40 (43.5)	1.59 [1.03; 2.43]	0.033	2.70 [1.35; 5.51]	0.006
Endocrinology/Nutrition	52 (85.2)	9 (14.8)	0.34 [0.15; 0.65]	0.003	0.74 [0.29; 1.81]	0.518
Oncology/Hematology	142 (81.1)	33 (18.9)	0.43 [0.29; 0.63]	<0.001	0.77 [0.39; 1.56]	0.465
Immunology/Vaccinology/Allergology	48 (80.0)	12 (20.0)	0.49 [0.25; 0.90]	0.029	0.84 [0.34; 2.00]	0.696
Gastroenterology/Hepatology	39 (67.2)	19 (32.8)	0.98 [0.55; 1.68]	0.933	1.79 [0.80; 3.99]	0.156
Infectious disease	102 (65.8)	53 (34.2)	1.05 [0.73; 1.48]	0.797	1.72 [0.89; 3.39]	0.109
Neurology	43 (65.2)	23 (34.8)	1.08 [0.63; 1.79]	0.781	1.84 [0.85; 3.99]	0.121
Nephrology	17 (60.7)	11 (39.3)	1.30 [0.59; 2.77]	0.496	2.69 [0.98; 7.29]	0.052
Pneumology	32 (61.5)	20 (38.5)	1.26 [0.71; 2.21]	0.420	2.48 [1.10; 5.66]	0.029

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Table 2 (Continued)

	Trials characteristics					
	Positive	Negative	Univariable OR [95% Confidence limits]	*P*	Multivariable OR [95% Confidence limits]	*P*
	n = 1,029	*n* = 513				
Psychiatry/Addictology	55 (75.3)	18 (24.7)	0.64 [0.36; 1.09]	0.112	0.91 [0.42; 1.96]	0.805
Pediatrics	112 (68.7)	51 (31.3)	0.90 [0.63; 1.27]	0.571	1.26 [0.66; 2.44]	0.491
Rheumatology/Musculoskeletal disorders	46 (67.6)	22 (32.4)	0.96 [0.56; 1.59]	0.870	1.98 [0.92; 4.29]	0.081
Dermatology	18 (85.7)	3 (14.3)	0.33 [0.08; 0.98]	0.077	0.95 [0.20; 3.47]	0.942

Data are expressed as number (corresponding percentage). [a]Each medical specialty was compared to all others.

Unexpectedly, the proportion of negative studies was not statistically related to trial registration. It is noteworthy that our study was not powered to test this hypothesis and a lack of statistical power cannot be excluded. Nonetheless, publication bias may occur during all stages of the publication process, from author submission and peer-review to editorial decision.[9] The development of prospective trial registration itself is not, therefore, sufficient to prevent publication bias. In a recent report, outcome switching was observed even for registered trials, showing that primary outcomes in publications were different from the latest registry entry version in 41% of trials.[15] In other words, trial registration in itself does not prevent publication bias or outcome switching, but it allows tracking of these two issues by increasing transparency. It is important to make sure that the results of registered trials are published in a peer-reviewed journal but authors might anticipate rejection by journals when they consider their results to be not important enough.[16] Our results do not support publication bias due to editorial decisions among the studied journals and are in line with a previously published study also performed in high-impact general medical journals that showed that the acceptance of submitted papers for publication by journals was not significantly associated with the direction or strength of their findings.[17] However, our results may have differed if we had examined lower-tier clinical journals with lower impact factors. Sponsors of negative trials might be hesitant to pursue publication in a high-impact journal due to concerns about rejection, and may instead opt to submit to a lower impact journal first. Other measures taken by journals and editors may have participated in reducing the existence and impact of publication bias. Consolidated Standards of Reporting Trials first published in 1996,[18] and progressively revised in 2001[19] and 2010[20] participated in harmonizing and improving the quality of reporting RCT over time.[21] This possibly increased the chances of publication in high-impact journals even in cases of negative results. The development of electronic journals without space limitation has exploded over the last decade allowing publishing more studies and electronic supplementary materials. It has been suggested that it should change editorial policies allowing clinical trials acceptation for publication, based not only on the impact of their findings but also on methodological criteria, and therefore encourage the publication of studies with negative or no significant results.[22]

Higher proportions of published negative trials in certain medical specialty could reflect an improvement of medical practices/therapeutics making it difficult to demonstrate treatment effects because new approaches must compete with higher-quality medical care.[23] In our study, this seems especially true in the fields of cardiology/vascular disease, emergency/critical care, obstetrics, surgery, and pneumology. Another explanation for the increase in negative trials could simply be the lack of efficacious new drugs in the pipelines.[24]

We also observed that negative studies were more likely to be superiority trials with a large sample size. Large RCT usually provide the best quality of evidence for new therapeutic evaluation and have shorter time to publication.[23,25] Therefore, researchers, sponsors, and editors may be more enthusiastic about the publication of these highly powered trials, even if they did not reach statistical significance.

As previously reported, we found that trials funded exclusively by private industries were more likely to be positive.[26] It is unlikely that this result reflects methodological bias. It has been shown that research methods and risks of bias of trials sponsored by drug companies are at least as good as those of academic-funded research.[26,27] Our data suggest however that the more frequent choice of inactive comparator in these studies could explain this result. This is in line with the importance of industry-sponsored RCT to demonstrate benefits for further treatment/device commercialization.[28] This may indicate that industry sponsors are cautious when designing studies and/or hesitant to publish negative results due to business considerations.

There are several limitations to be taken into consideration. First, we only included five publication years, which may give only a partial representative view of the past 20 years. Second, we searched for RCT published in only four general medical journals with high-impact factors. Our results may not reflect RCT published in the whole literature, especially in journals with specific areas of expertise. However, we chose high-impact journals that usually publish studies that may change medical practices. Given the design of our study, our results give predictive associations but we cannot affirm causality between the factors studied and negative trial results. There could be additional confounders (as change in research culture since 2000 for example) not considered here that might have influenced the number of trials conducted and reported during these years and are not accounted for in the analysis. In addition, results identified for secondary outcomes should be interpreted cautiously, as those analyses are exploratory and

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we did not use corrections for multiple tests. Finally, we did not compare published reports with their respective appended protocols declared in trial registries. Therefore, we cannot exclude the possibility of switching outcomes in non-registered studies (outcome bias) that might be different in registered and non-registered studies. This could yield to an overrepresentation of false positive results,[5,29] especially between 2000 and 2005 where the number of registered studies was low. Further work specifically focusing on drug intervention trials should also be conducted to assess the pharmacological reasons for trial failure.

Based on our results, the proportion of published negative studies in 2020 was higher only when compared to 2000. However, during the two decades, no trend was noticeable. It therefore remains unclear whether there is a relationship between trial registration and the publication of negative results over time. Expanding the range of journals to include a broader spectrum of clinical trial publications in future studies is likely to yield more comprehensive and complementary results.

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CONFLICT OF INTEREST

There are no conflicts of interest regarding this paper. (i) No authors have support from any company for the submitted work; (ii) FN has relationships (travel/accommodations expenses covered/reimbursed) with Servier, BMS, Lundbeck and Janssen, who might have an interest in the work submitted in the previous 3 years; no other authors have relationships with any company that might have an interest in the submitted work in the previous 3 years; (iii) No author's spouse, partner, or children have any financial relationships that could be relevant to the submitted work; and (iv) none of the authors has any non-financial interests that could be relevant to the submitted work. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

B.L., E.B., F.N., and J.-S.A. wrote the manuscript. B.L., E.B., and F.N. designed the research. C.Le., C.L.P., C.Po., C.Pa., J.-S.A., M.L., and P.C. performed the research. Q.L.C., C.Lo., J.-S.A., F.N., and B.L. analyzed the data.

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1. Cowley, A.J., Skene, A., Stainer, K. & Hampton, J.R. The effect of lorcainide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias. *Int. J. Cardiol.* **40**, 161–166 (1993).
2. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N. Engl. J. Med.* **321**, 406–412 (1989).
3. Cardiac arrhythmia suppression trial II investigators effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N. Engl. J. Med.* **327**, 227–233 (1992).
4. Olson, C.M. *et al*. Publication bias in editorial decision making. *JAMA* **287**, 2825–2828 (2002).
5. Dwan, K., Gamble, C., Williamson, P.R., Kirkham, J.J. & Reporting Bias Group. Systematic review of the empirical evidence of study publication bias and outcome reporting bias—an updated review. *PLoS One* **8**, e66844 (2013).
6. DeVito, N.J. & Goldacre, B. Catalogue of bias: publication bias. *BMJ Evid.-Based Med.* **24**, 53–54 (2019).
7. Dickersin, K. & Min, Y.I. NIH clinical trials and publication bias. *Online J. Curr. Clin. Trials* **50**, (1993).
8. Hopewell, S., Loudon, K., Clarke, M.J., Oxman, A.D. & Dickersin, K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst. Rev.* **2009**, MR000006 (2009).
9. Song, F. *et al*. Dissemination and publication of research findings: an updated review of related biases. *Health Technol. Assess. (Winch. Eng.)* **14**, iii, ix–xi, 1–193 (2010).
10. Registries, C. on C. T., Policy, B. on H. S. & Medicine, I. of Section 113 of the Food and Drug Administration Modernization Act of 1997 and Guidance for Industry: Information Programs on Clinical Trials for Serious or Life-Threatening Diseases and Conditions. U.S. Department of Health and Human Services March 2002. In *Dev. Natl. Regist. Pharmacol. Biol. Clin. Trials Workshop Rep*. (National Academies Press (US), 2006) < https://www.ncbi.nlm.nih.gov/books/NBK338089/>.
11. McCray, A.T. & Ide, N.C. Design and implementation of a national clinical trials registry. *J. Am. Med. Inform. Assoc.* **7**, 313–323 (2000).
12. Huser, V. & Cimino, J.J. Evaluating adherence to the International Committee of Medical Journal Editors' policy of mandatory, timely clinical trial registration. *J. Am. Med. Inform. Assoc.* **20**, e169–e174 (2013).
13. De Angelis, C. *et al*. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N. Engl. J. Med.* **351**, 1250–1251 (2004).
14. WHO Statement on public disclosure of clinical trial results < https://www.who.int/news/item/09-04-2015-japan-primary-registries-network>.
15. Holst, M., Haslberger, M., Yerunkar, S., Strech, D., Hemkens, L.G. & Carlisle, B.G. Frequency of multiple changes to prespecified primary outcomes of clinical trials completed between 2009 and 2017 in German university medical centers: a meta-research study. *PLoS Med.* **20**, e1004306 (2023).
16. Weber, E.J., Callaham, M.L., Wears, R.L., Barton, C. & Young, G. Unpublished research from a medical specialty meeting: why investigators fail to publish. *JAMA* **280**, 257–259 (1998).
17. Lee, K.P., Boyd, E.A., Holroyd-Leduc, J.M., Bacchetti, P. & Bero, L.A. Predictors of publication: characteristics of submitted manuscripts associated with acceptance at major biomedical journals. *Med. J. Aust.* **184**, 621–626 (2006).
18. Begg, C. *et al*. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* **276**, 637–639 (1996).
19. Altman, D.G. *et al*. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann. Intern. Med.* **134**, 663–694 (2001).
20. Schulz, K.F., Altman, D.G., Moher, D. & CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *BMC Med.* **8**, 18 (2010).
21. Turner, L. *et al*. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomized controlled trials (RCTs) published in medical journals. *Cochrane Database Syst. Rev.* **11**, MR000030 (2012).
22. Song, F., Eastwood, A., Gilbody, S. & Duley, L. The role of electronic journals in reducing publication bias. *Med. Inform. Internet Med.* **24**, 223–229 (1999).
23. Kaplan, R.M. & Irvin, V.L. Likelihood of null effects of large NHLBI clinical trials has increased over time. *PLoS One* **10**, e0132382 (2015).

15326535, 2025, 3, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3535 by Cochrane France, Wiley Online Library on [23/09/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

24. Cottingham, M.D., Kalbaugh, C.A. & Fisher, J.A. Tracking the pharmaceutical pipeline: clinical trials and global disease burden. *Clin. Transl. Sci.* **7**, 297–299 (2014).
25. Gordon, D., Taddei-Peters, W., Mascette, A., Antman, M., Kaufmann, P.G. & Lauer, M.S. Publication of trials funded by the National Heart, Lung, and Blood Institute. *N. Engl. J. Med.* **369**, 1926–1934 (2013).
26. Lundh, A., Lexchin, J., Mintzes, B., Schroll, J.B. & Bero, L. Industry sponsorship and research outcome. *Cochrane Database Syst. Rev.* **2**, MR000033 (2017).
27. Bekelman, J.E., Li, Y. & Gross, C.P. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* **289**, 454–465 (2003).
28. Flacco, M.E. *et al*. Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor. *J. Clin. Epidemiol.* **68**, 811–820 (2015).
29. Raghav, K.P.S. *et al*. From protocols to publications: a study in selective reporting of outcomes in randomized trials in oncology. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **33**, 3583–3590 (2015).

15326535, 2025, 3, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3535 by Cochrane France, Wiley Online Library on [23/09/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License