

Characteristics of Depression Clinical Trials Registered on ClinicalTrials.gov

Juan Liang¹, Peijie He¹, Hanting Wu¹, Xiujuan Xu², Conghua Ji^{1,3} 

¹School of Public Health, Zhejiang Chinese Medical University, Hangzhou, 310053, People's Republic of China; ²Tongde Hospital of Zhejiang Province, Hangzhou, 310012, People's Republic of China; ³The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, 310006, People's Republic of China

Correspondence: Conghua Ji, Email jchi2005@126.com

Background: Mental disorders are among the leading causes of the global health-related burden, and depression is one of the most disabling mental disorders. The emergence of the COVID-19 pandemic has created an environment where many determinants of mental health are exacerbated. Many studies have been registered and conducted over the past 16 years, but how to choose the proper design for depression clinical trials remains the main concern. This study aimed to characterize the current status of global depression clinical trials registered on ClinicalTrials.gov.

Methods: We examined all the trials registered on ClinicalTrials.gov from 2007 to 2021.

Results: Overall, 7623 depression clinical trials were identified for analysis. Of those trials, 6402 (83.98%) were intervention trials and 1212 (15.90%) were observational trials. The majority of intervention types were behavioral (35.2%) and drug (28.55%), with very few procedures, dietary supplements, and diagnostic test studies. In addition, 55.53% of trials enrolled <100 participants. The proportions of trials registered in North America were higher than on other continents. Furthermore, the trials that involved only females (12.6%) were more than only males (0.87%) from 2019 to 2021.

Conclusion: Depression clinical trials registered on ClinicalTrials.gov were dominated by small sample size trials, and there is a lack of trials related to COVID-19. The choice of study design is crucial, and properly designed trials can help improve study efficiency and reduce the likelihood of study failure. Given the increased number of RCT trials, the trial quality is gradually improving over the years. In addition, depression trials concentrating on children and older adults need more scientific attention. Further studies related to COVID-19 are needed, given the great damage that causes to people's physical and mental health.

Keywords: depression, ClinicalTrials.gov, characteristics of depression clinical trials

Introduction

Depression¹ is one of the critical mental disorders, characterized by high morbidity, high disability, high recurrence rate, and high suicide rate. Commonly, the main clinical characteristics of these patients are persistently low mood in which there is a feeling of sadness and loss of interest. Severe psychotic depression is often accompanied by cognitive and neurovegetative symptoms, such as difficulty in concentrating, memory alterations, anorexia, and sleep disturbances.² For depression patient, symptoms persist over the long term and, when more severe, can impair quality of life and function.³ The proportion of the global population living with depression is estimated to be 322 million people—4.4% of the world's population according to a new report, released by the World Health Organization.⁴ The Global Burden of Disease Study (GBD) 2017 revealed that depressive disorders are ranked as the third leading cause of “years lived with disability” worldwide,⁵ and the most disabling mental disorder was depressive, which ranked among the top 25 leading causes of burden worldwide in 2019.⁶

Numerous reports mentioned that depressive symptoms and fear have increased during the COVID-19 pandemic.⁷ A recent poll has shown that a significant number of Americans live in fear of the disease and COVID-19's consequences.⁸ Some research indicates that family members who lost family or friends owing to COVID-19 can display acute post-traumatic stress disorder in which emotional numbness and insomnia are prevalent,⁹ and this condition

may trigger the onset of depression. According to the report, long working hours, untimely emergency calls, a quarantined state, and separation from family and friends due to professional commitments put healthcare providers under extreme stress, anxiety, and frustration.¹⁰ All these factors greatly increase the risk of depression.

Usually, depression can be assessed using a dimensional approach, through self or clinician-rated questionnaires,¹¹ such as the Hamilton Depression Rating Scale (HAM-D17, 21, 24 items),¹² the Montgomery-Åsberg Depression Rating Scale (MADRS10),¹³ and the Quick Inventory of Depressive Symptomatology (QIDS) Clinician Rating (QIDS-C).¹⁴ Clinical trials generate important data on disease recognition and treatment, which can have significant medical, financial, and political implications. Yet, the search on depression may have been limited by the methodological heterogeneity of studies, leading to several published recommendations of ways to optimize clinical trial methodology in this field.¹⁵ The International Committee of Medical Journal Editors (ICMJE) advocated that clinical trials should be registered in a public registry before participants were recruited to ensure process transparency and legality.¹⁶ The ClinicalTrials.gov database provides the most comprehensive information about ongoing and completed clinical studies worldwide.¹⁷ As clinical trials are considered the gold standard for evaluating the safety and efficacy of therapeutics and generating evidence-based knowledge in medicine,¹⁸ a growing number of clinical studies have been conducted to examine the scientific evidence of depression. Conducting depression clinical trials is important to improve disease management. However, there is a lack of thorough evaluation of depression clinical trials. Thus, a better understanding of the current features of depression clinical trials is important for improving clinical trial designs and identifying neglected research areas. This understanding will improve the translatability of results into benefits for patients. The current analysis aims to describe the depression trial portfolio using ClinicalTrials.gov data, including trial attributes, enrollment, study design, location, and sponsor. Secondly, we aim to compare the relationship between depression interventions and medical conditions and describe trends in depression trials over time.

Materials and Methods

Data Sources and Search

We searched the database of ClinicalTrials.gov with the keyword “depression” without restriction on languages and study type. The earliest data were generated from 2006, for convenience in grouping and statistical analysis, the search time was limited from January 1, 2007 to December 30, 2021. The registration information of all relevant trials was downloaded. All available results were downloaded as XML files. Subsequently, all data was imported into an Excel form to facilitate further data selection, classification, and management.

Data Extraction

As previously described, trial data were self-reported by trial sponsors or investigators by using a web-based system. Data related to the following variables were independently extracted by two investigators from the downloaded registration information files, after which a third researcher checked the data. The following information was collected from each study: title, date of registration, locations, study type, study design, interventions and control, sponsor and collaborators, phases, sample size, outcomes, and recruiting status. The overall status of registered clinical trials on depression were reviewed and collated.

Study type was categorized as interventional, observational, and unknown. Study design was more refined and includes allocation: N/A, allocation: randomized, allocation: non-randomized, case-control, cohort, ecologic/community, family-based, other, and unknown. Patients' age was classified as child, adult, and old adult. In terms of the type of intervention, device is a treatment device for depression and procedure is the diagnostic procedure of depression. If the original data is blank, we define it as “unknown”. The original data is incomplete and it is failure to know what “other” includes.

Data Analysis

We analyzed depression data for 2007–2021 and found a dramatic increase in depression clinical trial registrations after 2019, we decided to evaluate registrations for 2019–2021 to examine depression trials methodology.

We reported absolute numbers and percentages for categorical variables and compared them by using χ^2 analysis. Analyses were conducted on gender, age, enrollment, design, study type, and locations.

Results

General Characteristics of Registered Trials

From January 1, 2007, to December 30, 2021, a total of 7623 registered clinical trials were retrieved from the Clinicaltrials.gov database. We found an increasing number of trials registered for depression from 2007 to 2021. There were 355 trials in 2007–2009, 557 trials in 2010–2012, 1162 trials in 2013–2015, 1772 trials from 2016–2018, and 3777 trials in 2019–2021. Furthermore, there is a dramatic increase in the number of trials from 2016 to 2021 (Table 1 and Figure 1). The proportion of drug intervention trials decreased over time: from 54.37% in 2007–2010 to 19.94% in 2019–2021. Behavioral intervention trials are increasing in importance because of an increasing proportion of the intervention types from 2007 to 2021: from 15.77% in 2007–2010 to 39.95% in 2019–2021. In addition, there were more behavioral trials (39.95%) than drug trials (19.94%) in 2019–2021. At the same time, the proportion of devices was 11.41%, for example, brain stimulation, which is a potential treatment for non-treatment resistant depression.¹⁹ Most depression trials (55.53%) were small sample sizes, enrolling <100 subjects, although some of the trials had an anticipated enrollment of 5000 or more participants (1.50%) in 2007–2021. A substantial proportion of depression studies were interventional (82.5%), and the proportion of observational experiments was only 17.29% in 2019–2021. The majority of depression trials were in North America (52.18%), and the second was in Europe (21.55%) which is more than in Asia and South America (12.97% and 1.84%) from 2007 to 2021. And there was a subtle increase in the

Table 1 Characteristics of All Included Studies

	2007–2009 (N=355)	2010–2012 (N=557)	2013–2015 (N=1162)	2016–2018 (N=1772)	2019–2021 (N=3777)	ALL (N=7623)
Type of intervention, n (%)						
Behavioral	56 (15.77)	129 (23.16)	405 (34.85)	584 (32.96)	1509 (39.95)	2683 (35.20)
Drug	193 (54.37)	253 (45.42)	389 (33.48)	588 (33.18)	753 (19.94)	2176 (28.55)
Device	21 (5.92)	27 (4.85)	82 (7.06)	146 (8.24)	431 (11.41)	707 (9.27)
Procedure	14 (3.94)	25 (4.49)	43 (3.70)	31 (1.75)	55 (1.46)	168 (2.20)
Dietary Supplement	2 (0.56)	16 (2.87)	15 (1.29)	33 (1.86)	63 (1.67)	129 (1.69)
Diagnostic Test	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.28)	48 (1.27)	53 (0.70)
Unknown	45 (12.68)	58 (10.41)	111 (9.55)	154 (8.69)	298 (7.89)	666 (8.74)
Other	24 (6.76)	49 (8.80)	117 (10.07)	231 (13.04)	620 (16.42)	1041 (13.66)
Enrollment, n (%)						
0–100	194 (54.65)	327 (58.71)	576 (49.57)	1091 (61.57)	2045 (54.14)	4233 (55.53)
101–500	120 (33.80)	168 (30.16)	440 (37.87)	530 (29.91)	1280 (33.89)	2538 (33.29)
501–1000	25 (7.04)	44 (7.90)	88 (7.57)	70 (3.95)	193 (5.11)	420 (5.51)
1001–5000	14 (3.94)	14 (2.51)	43 (3.70)	64 (3.61)	183 (4.85)	318 (4.17)
>5001	2 (0.56)	4 (0.72)	15 (1.29)	17 (0.96)	76 (2.01)	114 (1.50)
Study type, n (%)						
Interventional	297 (83.66)	475 (85.28)	1002 (86.23)	1512 (85.33)	3116 (82.50)	6402 (83.98)
Observational	58 (16.34)	82 (14.72)	160 (13.77)	259 (14.62)	653 (17.29)	1212 (15.90)
Unknown	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.06)	8 (0.21)	9 (0.12)
Locations, n (%)						
North America	178 (50.14)	256 (45.96)	648 (55.77)	970 (54.74)	1926 (50.99)	3978 (52.18)
Europe	78 (21.97)	142 (25.49)	217 (18.67)	351 (19.81)	855 (22.64)	1643 (21.55)
Asia	40 (11.27)	84 (15.08)	150 (12.91)	167 (9.42)	548 (14.51)	989 (12.97)
South America	6 (1.69)	16 (2.87)	22 (1.89)	33 (1.86)	63 (1.67)	140 (1.84)
Africa	6 (1.69)	2 (0.36)	4 (0.34)	22 (1.24)	56 (1.48)	90 (1.18)
Oceania	9 (2.54)	11 (1.97)	23 (1.98)	12 (0.68)	11 (0.29)	66 (0.87)

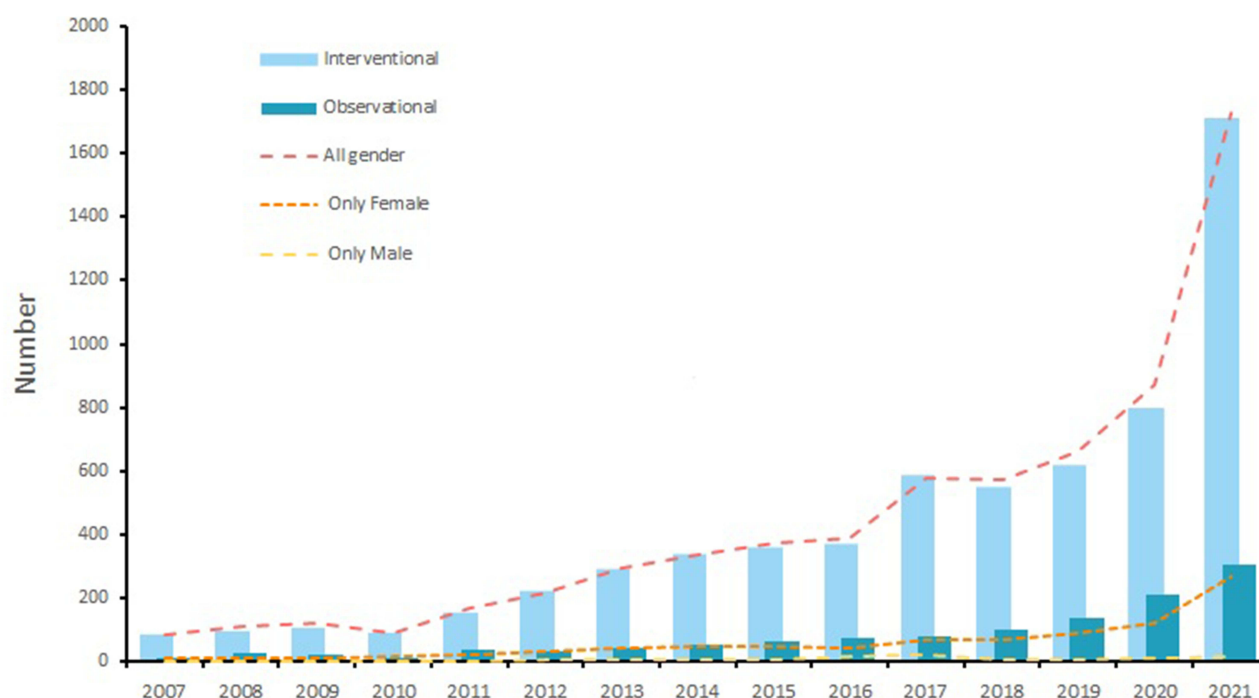


Figure 1 The trend of registered depression studies on ClinicalTrials.gov.

proportion of trials in Asia: from 11.27% in 2007–2010 to 14.51% in 2019–2021, and the proportion in North America increased from 45.96% to 50.99%.

Montgomery-Asberg Depression Rating Scale, Quick Inventory of Depressive Symptoms (QIDS), Hamilton Anxiety Rating Scale (HAM-A) and Clinical Global Impression of Severity (CGI-S) were mainly used as outcome measures in the included depression trials.

Table 2 summarized the trials design characteristics for depression trials in 2019–2021. The total number of depression trials registered was 3777. There was a great increase in the number: from 757 in 2019 to 1006 in 2020 and 1014 in 2021.

Table 2 In-Depth Study Characteristics of Depression Studies in 2019–2021

	ALL (N=3777)	2019 (N=757)	2020 (N=1006)	2021 (N=1014)	P-value
Age*, n (%)					
Children	557 (14.75)	112 (14.80)	152 (15.11)	293 (14.55)	0.919
Adult	3537 (93.65)	712 (94.06)	947 (94.14)	1878 (93.25)	0.561
Old adult	2795 (74.00)	562 (74.24)	743 (73.86)	1490 (74.98)	0.983
Gender, n (%)					
All	3258 (82.26)	660 (87.19)	872 (86.68)	1726 (85.70)	0.541
Female	476 (12.60)	89 (11.76)	120 (11.93)	267 (13.26)	0.430
Male	33 (0.87)	5 (0.66)	11 (1.09)	17 (0.84)	0.613
Unknown	10 (0.26)	3 (0.40)	3 (0.30)	4 (0.20)	0.646
Study type, n (%)					
Interventional	3116 (82.50)	618 (81.64)	794 (78.93)	1704 (84.61)	<0.001
Observational	653 (17.29)	137 (18.10)	209 (20.78)	307 (15.24)	0.001
Unknown	8 (0.21)	2 (0.26)	3 (0.30)	3 (0.15)	0.660
Is it related to COVID-19? n (%)					
Yes	140 (3.71)	0 (0.00)	58 (5.77)	82 (4.07)	<0.001
No	3637 (96.29)	757 (100.00)	948 (94.23)	1932 (95.93)	<0.001

Note: *There are multiple subjects in one study, therefore the statistical values are repeated.

Within 3777 depression trials, the intervention studies were much more than the observational studies, and the number of interventional studies and observational studies were 3116 (82.50%) and 653 (17.29%), respectively. Most depression trials involved adults (93.65%), and 14.75% involved children (14.75%). Furthermore, a great part of depression trials involved all gender (82.26%). It was obvious that more trials involved only females (12.60%) than only males (0.87%) in depression experiments (Figure 1). And the proportion of trials involving only females increased from 11.76% to 13.36%, and trials that involved only males increased from 0.66% to 0.84%. Among all the clinical trials, there were 140 (3.7%) trials related to COVID-19.

Study Design of Registered Trials

Table 3 compares the study design of interventional studies (3122,82.66%) and observational studies (646,17.1%) in 2019–2021. Interventional trials were classified into four categories: allocation: N/A, allocation: randomized, allocation: non-randomized and unknown, and observational trials which means non-randomized comparative studies were classified into six categories: case-control, cohort, ecologic/community, family-based, other and unknown. The proportion of interventional studies increased from 81.77% to 84.76% and observational studies decreased from 17.17% to 15.24%. Randomized allocation studies (2430,77.83%) accounted for the largest part of the interventional studies, and there were 337 (52.17%) cohort studies in the observational studies. Comparing four categories of depression interventional trials from 2019 to 2021, N/A allocation studies increased from 12.81% to 14.35%; randomized allocation studies increased from 62.75% to 65.54%; non-randomized allocation studies decreased from 6.08% to 4.87%.

Table 3 Design of Depression Studies in 2019–2021

Design	2019 (N=757)	2020 (N=1006)	2021 (N=2014)	P-value
Intervention Studies	619 (81.77)	796 (79.13)	1707 (84.76)	<0.001
Allocation: N/A	97 (12.81)	112 (11.13)	289 (14.35)	0.187
Intervention Model: Single Group Assignment	97 (12.81)	111 (11.03)	289 (14.35)	
Intervention Model: Sequential Assignment	0 (0.00)	1 (0.10)	0 (0.00)	
Allocation: Randomized	475 (62.75)	635 (63.12)	1320 (65.54)	0.298
Intervention Model: Parallel Assignment	416 (54.95)	550 (54.67)	1147 (56.95)	
Intervention Model: Crossover Assignment	33 (4.36)	45 (4.47)	82 (4.07)	
Intervention Model: Single Group Assignment	9 (1.19)	8 (0.80)	28 (1.39)	
Intervention Model: Factorial Assignment	13 (1.72)	23 (2.29)	43 (2.14)	
Intervention Model: Sequential Assignment	4 (0.53)	9 (0.89)	19 (0.94)	
Unknown	0 (0.00)	0 (0.00)	1 (0.05)	
Allocation: Non-Randomized	46 (6.08)	49 (4.87)	98 (4.87)	0.326
Intervention Model: Parallel Assignment	30 (3.96)	38 (3.78)	74 (3.67)	
Intervention Model: Single Group Assignment	10 (1.32)	5 (0.50)	9 (0.45)	
Intervention Model: Crossover Assignment	2 (0.26)	4 (0.40)	5 (0.25)	
Intervention Model: Sequential Assignment	3 (0.40)	2 (0.20)	9 (0.45)	
Intervention Model: Factorial Assignment	1 (0.13)	0 (0.00)	1 (0.05)	
Unknown	1 (0.13)	0 (0.00)	0 (0.00)	0.132
Observational studies	130 (17.17)	209 (20.78)	307 (15.24)	0.001
Observational Model: Cohort	66 (8.72)	108 (10.74)	163 (8.09)	
Observational Model: Case-Control	42 (5.55)	52 (5.17)	95 (4.72)	
Observational Model: Other	11 (1.45)	40 (3.98)	35 (1.74)	
Observational Model: Ecologic or Community	4 (0.53)	7 (0.70)	13 (0.65)	
Observational Model: Family-Based	1 (0.13)	2 (0.20)	1 (0.05)	
Unknown	6 (0.79)	0 (0.00)	0 (0.00)	
Unknown	8 (1.06)	1 (0.10)	0 (0.00)	<0.001

Locations of Registered Trials

According to the statistics, from 2007 to 2021, North America (52%) accounts for the largest proportion, followed by Europe (22%) (Figure 2). Table 4 demonstrates the locations of registered depression trials in 2019–2021. The total number of registered trials in the three years was 757, 1006, and 1014 respectively. Comparing the six continents of the world from 2019 to 2021, the number of trials in North America has increased from 383(50.59%) to 1006(52.93%); the number of trials in Europe has increased from 163(21.53%) to 447(22.19%); the trials number of Asia has increased from 118(15.59%) to 267 (13.26%). In 2019–2021, most depression trials were in North America in 1926(50.99%), and the United States accounts for 82.81% of them. In addition, the number in Europe and Asia were 855(22.64%) and 548 (14.51%). As is shown in Table 4, 163(21.53%) trials belonged to Europe in 2019, and Europe studies accounted for a proportion (24.35%) of clinical trials launched in 2020 and gradually decreased. Chinese takes the largest (242,44.16%) accounting for part of the Asia depression trials.

Discussion

This analysis provides a snapshot of the landscape of depression clinical trials registered on ClinicalTrials.gov, which results provide the basis for the treatment and prevention of diseases within depression, as well as the characteristics of trial design, location, and intervention type.

Depression trials accounted for a growing proportion of all medical trials (Table 5). There is an urgent need for more effective treatment of depression, not only the disorder is becoming more common, but also it is associated with major health and economic burdens.²⁰ In this study, by comparing essential key characteristics of proper testing and development of depression experiments, several noteworthy observations emerged. We found that depression trials were small in scale, and the majority of studies (55.53%) on ClinicalTrials.gov typically enrolled 100 or fewer patients, and only several studies (1.5%) enrolled 5000 and more patients. Typically, small studies have a high risk of type II error, that is failure to reject the null hypothesis and inappropriately concluding that a treatment or intervention is ineffective when the sample size is too small to determine a significant effect.^{21,22} These findings raise concerns that the growing depression patient population may still not be receiving the attention, funding, or efforts necessary to identify new therapies.

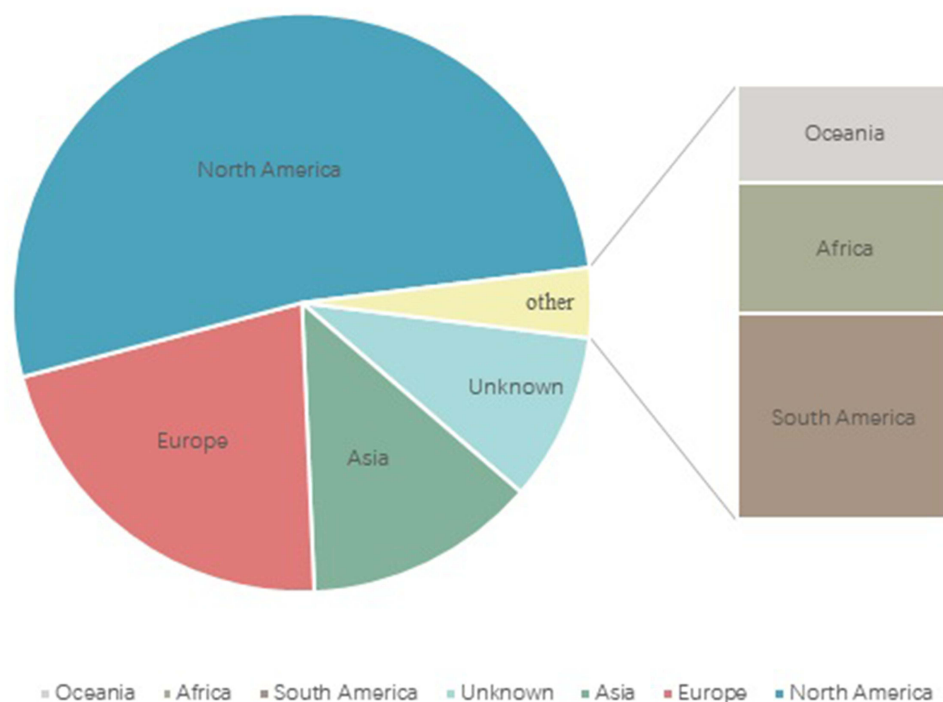


Figure 2 Locations of depression studies from 2007 to 2021.

Table 4 Locations of Depression Studies

Locations	2019(N=757)	2020(N=1006)	2021(N=2014)	P-value
North America	383 (50.59)	477 (47.42)	1066 (52.93)	0.016
United States	323 (42.67)	399 (39.66)	873 (43.35)	
Canada	55 (7.27)	68 (6.76)	175 (8.69)	
Other	5 (0.66)	10 (0.99)	18 (0.89)	
Europe	163 (21.53)	245 (24.35)	447 (22.19)	0.294
United Kingdom	24 (3.17)	39 (3.88)	68 (3.38)	
France	21 (2.77)	34 (3.38)	72 (3.57)	
Germany	21 (2.77)	30 (2.98)	57 (2.83)	
Spain	20 (2.64)	24 (2.39)	50 (2.48)	
Other	77 (10.17)	118 (11.73)	200 (9.93)	
Asia	118 (15.59)	163 (16.20)	267 (13.26)	0.061
China	59 (7.79)	65 (6.46)	118 (5.86)	
Mainland	36 (4.76)	44 (4.37)	67 (3.33)	
Taiwan	16 (2.11)	11 (1.09)	24 (1.19)	
Hong Kong	7 (0.92)	10 (0.99)	27 (1.34)	
Turkey	8 (1.06)	31 (3.08)	53 (2.63)	
Other	51 (6.74)	67 (6.66)	96 (4.77)	
South America	11 (1.45)	15 (1.49)	37 (1.84)	0.685
Brazil	8 (1.06)	9 (0.89)	21 (1.04)	
Chile	2 (0.26)	2 (0.20)	9 (0.45)	
Other	1 (0.13)	4 (0.40)	7 (0.35)	
Africa	13 (1.72)	8 (0.80)	35 (1.74)	0.109
Egypt	4 (0.53)	5 (0.50)	14 (0.70)	
Other	9 (1.19)	3 (0.30)	21 (1.04)	
Oceania	1 (0.13)	8 (0.80)	2 (0.10)	0.002
Australia	1 (0.13)	7 (0.70)	2 (0.10)	
Zealand	0 (0.00)	1 (0.10)	0 (0.00)	
Unknown	68 (8.98)	90 (8.95)	160 (7.94)	0.532
Total	757 (100.00)	1006 (100.00)	2014 (100.00)	

Table 5 The Percentage of Depression Trials in All Medical Trials

	2007–2009	2010–2012	2013–2015	2016–2018	2019–2021
Depression research	355	557	1162	1772	3777
All medical research	44,103	54,988	66,697	82,835	96,805
Depression research/All medical research	0.80%	1.01%	1.74%	2.14%	3.90%

The statistics in our analysis also showed that interventional studies accounted for the largest portion of clinical trials on depression in the last 3 years, and most interventional trials in depression are on non-responsive depression.²³ Although the observational type is also important for generating hypotheses, properly designed RCTs are needed to substantiate effective therapies.²² In contrast, observational studies were decreased because they often summarize and analyze the existing clinical data in clinical work in a retrospective way, and researchers did not randomize patients to control intervention measures.²⁴ Appropriate selection of study design is only one element of a successful study. The choice of study design should take into account cost, access to cases, identification of exposures, epidemiologic measures needed, and the current level of published evidence on the particular exposure-outcome relationship being evaluated.²⁵

We classified medical conditions to examine links between depression interventions and conditions. It shows that depression trials were significantly more likely to focus on behavioral trials than drug trials. Overall, almost 60% of depression trials focus on two therapeutic areas. Some prior reviews have reported that cognitive behavioral therapy as

a first-line psychological treatment can effectively improve the symptoms of moderate depression.²⁶ The maximal proportion of behavioral intervention trials was 39.95%, and drug intervention accounted for only 19.94% in the same period. In the past six years, Although the quantity of trials has increased sharply, the proportion of behavioral intervention was increased, but drug intervention was decreased. During the pandemic, most trials temporarily ceased recruitment.²⁷ But online assessments are becoming increasingly popular.²⁸ Thus, it was feasible to recruit and deliver behavioral interventions online.

Through a contemporary review of clinical trials registered for depression, the current findings show that an increasing number of depression trials are available at ClinicalTrials.gov, especially in the United States. It indicates the high priority given to depression by researchers in the United States, which remains the country with the most depression clinical trials conducted, followed by Canada. On the one hand, the incidence rate of depression is the highest in the United States, which is 16.1%.^{29,30} On the other hand, the United States, as a developed country, ranks first in the world in terms of investment in scientific research.³¹

In addition, a notable finding is the 32% and 100% growth rates in the number of trials from 2019 to 2020 and 2020 to 2021. This figure indicates an explosive growth in depression trials worldwide in 2021. Also, COVID-19-related studies in depression trials start to appear and gradually increase in 2020. This could be due to two reasons. First, from the latest published article, the prevalence of depression increased to 4, 802.4/100,000 after the COVID-19 outbreak, which means that 374 million people in the world are suffering from depression. In other words, the pandemic increased the prevalence of depression by about 76 million in 2020. In 2021, there are more than 350 million people with depression worldwide.^{6,32} That means it is imperative to conduct more research related to depression, such as providing useful tools and recommendations for improving the efficiency, quality, monitoring, and reporting of clinical trials.³³

It should be noted that the largest proportion of trials was conducted on adults, followed by the elderly. In addition, we found that some subjects were children. Nationally, representative, epidemiological studies have shown that the lifetime prevalence of depression among adolescents aged 15 to 18 years ranges from 11% to 14%. It is also estimated that approximately half of the first episodes of depression occurred during adolescence.³⁴ These articles suggest that a large proportion of adolescents will suffer from depression during their formative years.^{35,36} In addition, within the last 3 years, the proportion of trials in females was much higher than in males, as the prevalence of depression and anxiety was higher in women than in men worldwide before COVID-19.⁶ Women's psychology is more vulnerable to social and economic changes. Compared with men, women are about twice as likely to suffer from depression.³⁷ During their reproductive years, women are 1.5 to 3 times more likely to suffer from current and lifetime unipolar depression than men.³⁸ Since COVID-19, the differences in depression and anxiety disorders between men and women have been further amplified.³⁹ Therefore, it is necessary to pay more attention to the research on female depression.

While our study is unique, it has some limitations. For trials with fewer than 100 participants, it was difficult to identify how many of these trials were explicitly registered as pilots or feasibility trials. Information was not available on whether the female-only trials were conducted among patients with postpartum depression or postmenopausal women. ClinicalTrials.gov does not include all trials conducted worldwide. In addition, trials may not be included in our analysis if essential elements or keywords were not included at the time of registration. Misclassification may lead to some inappropriate conclusions. However, our study process attempted to minimize these potential biases. Trial design, implementation, and results must be transparent, and then the results must be rapidly disseminated to clinical practice.

Conclusions

In summary, our research suggests that temporary depression trials are not only small in sample size but also the number of trials. With the increase in the number of depressed patients in recent years, more comprehensive trials are urgently needed. First of all, the choice of study design is crucial, properly designed trials can help improve study efficiency and reduce the likelihood of study failure. Given the increased number of RCT trials, the trial quality is gradually improving over the years. Secondly, depression trials concentrating on children and older adults need more scientific attention. Further studies related to COVID-19 are needed, given the great damage that causes to people's physical and mental health.

Data Sharing Statement

This study is based on a public database and is not suitable for the approval of the ethics committee.

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Authors' contributions: C.H.J., and J.L. were responsible for the concept and design of the study; X.J.X., P.J.H., and H.T.W. were responsible for data acquisition; H.T.W., X.J.X., and J.L. were responsible for statistical analysis; C.H.J. and J.L. were responsible for the interpretation of results, and C.H.J. and J.L. analyzed the data and drafted the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no financial or other conflicts of interest.

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