Societal well-being is reflected in outcomes of antidepressant clinical trials.

Alexander Lebedev (alexander.lebedev@ki.se)
Karolinska Institutet https://orcid.org/0000-0002-0319-2357
Kasim Acar
Karolinska Institutet
Walter Osika
Karolinska Institutet https://orcid.org/0000-0002-1583-7319
Otto Simonsson
Karolinska Institutet
Morten Kringelbach
University of Oxford https://orcid.org/0000-0002-3908-6898
Gustavo Deco
Center for Brain and Cognition, Universitat Pompeu Fabra, Barcelona https://orcid.org/0000-0002-8995-7583
Martin Ingvar
Karolinska Institute
Predrag Petrovic
Karolinska Institutet https://orcid.org/0000-0002-5536-945X

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Abstract

Objective

Placebo effect has been found to be a significant contributor to the outcomes of antidepressant treatment, leading to questions about its overall efficacy. Previous research has shown that global societal trends and events such as economic recessions and pandemics, significantly affect people's mental health. The relationship between the two has not previously been examined. The present study investigated how global social sentiment, as indexed by global suicide rates, is related to the the treatment response in clinical trials of antidepressants.

Methods

We scrutinized data from a 1979–2016 meta-analysis of antidepressant clinical trials for depression. Outcomes from placebo and active groups, including responders, remitters, and dropouts, were matched with annual global suicide rates. Linear and non-linear methods were leveraged to estimate effect-sizes.

Results

During periods with high suicide rates, placebo groups displayed fewer responders ($r=-0.38, P < 0.001$) and remitters ($r=-0.42, P < 0.001$), and a higher dropout rate ($r = 0.56, P < 0.001$). Active groups exhibited a similar pattern, but the placebo arms were affected more strongly. The findings held true after applying non-linear methods, alternative metrics, and accounting for initial depression severity, group size, publication year, trial duration, proportion of multi-center studies. Specificity analyses revealed that earlier suicide rates had stronger association with the trial outcomes, and in a subsample of studies conducted in North America suicide rates from more culturally distant countries had weaker association with the outcomes.

Conclusions

The placebo effects observed in antidepressant treatment are influenced by societal wellbeing, suggesting that socionomic sentiment should be taken into account when assessing the effectiveness of psychopharmacological interventions.

Introduction

The evaluation of drug efficacy through the classical model relies on comparing active medications and placebo treatments in clinical randomized controlled trials (RCTs). Such comparisons necessitate a meticulous examination of the nature and magnitude of placebo responses, particularly concerning their dependence on intrinsic and extrinsic factors, such as patient characteristics and trial contexts.

The role of placebo effects in clinical trials of antidepressant medications has been a topic of enduring debate, with researchers yet to reach a consensus on their impact on clinical outcomes and treatment efficacy. While the majority of authors concur that the placebo effect in these trials is substantial (accounting for 35% and 40% of the total response (1)), some argue that the active drug provides minimal or no additional benefit (2–4). This has been challenged by other research teams, who have found that the effect of the active drug is much more significant when depressed mood is measured as a continuous variable (5). In support of this perspective, a recent meta-analysis substantiated the consistent efficacy of antidepressant medications in the treatment of depression (6).

There is also evidence that the strength of the placebo response may vary (7). For instance, previous research has identified a robust association between baseline depression severity and placebo effects, indicating that the placebo response is diminished in individuals experiencing more severe depression (2, 3, 8). Such effects have direct implications for comparisons with active antidepressant treatments. Despite suggestions of a general increase in the placebo response over time in studies of antidepressant treatment, no such effect has been noted after careful analysis of data collected over a period of 30 years that took into account confounding effects of trial duration and the preponderance of single-center studies (1).

The experimental induction of a placebo effect involves introducing a positive expectation without the use of an active treatment, but even in the presence of active treatment, such manipulations can significantly influence study outcomes (9).

The potency of a placebo response hinges on the trustworthiness of the manipulation, which could potentially be more easily achieved during periods of favorable global societal sentiment, marked by a better social and economic climate. Durkheim's seminal work on social integration and its impact on individuals' mental health has played a crucial role in shaping the trajectory of modern research on the social aspects of mental health. Of particular relevance to the present study, Durkheim posited that suicide rates are inversely related to the degree of social integration within a society (10), which, in turn, may substantially dictate the context in which therapeutic interventions occur. It is now widely recognized that periods of social and economic unrest are strongly associated with people's well-being, as evidenced by behavioral patterns and health metrics such as substance use, suicides and self-harm, number of fatal car accidents, blood pressure, mood and even neuroanatomical and functional characteristics of the affective brain (11–15). These effects mirror the consequences of pandemics and natural disasters (16, 17). A concept of "social mood" related to Durkheim's ideas was introduced more recently as a possible explanation for these relationships. According to this theory, social mood is a result of herd behavior that emerges from population dynamics and has a significant influence on global events, such as economic crises, wars, and cultural trends. (15, 18, 19).

Building on these findings, the present study aimed to investigate the extent to which the outcomes of psychopharmacological interventions for depression, including both active drug and placebo treatment, may be dependent on social context as indexed by global suicide rates.

Methods

Data: Clinical Trials

The present study utilized a dataset of 522 double-blind, parallel-group, randomized clinical trials by Cipriani et al., 2018 (6), which includes a total of 522 double-blind, parallel-group, randomized clinical trials conducted over a period of 37 years, between 1979 and 2016. The original meta-analysis was focused on comparative efficacy of 21 antidepressants investigated in the afore-mentioned trials, and contained a total of 1199 data entries. The present analyses prioritized placebo response for interpretability reasons due to a wide range of different active drugs used in clinical trials over the investigated period.

Following the exclusion of 232 entries lacking a publication year, we obtained a final dataset comprising 429 unique trials (Fig. 1).

Data: Socionomic Sentiment

As a proxy measure of social mood, the study leveraged official statistics on global suicide rates accessed from The Organization for Economic Co-operation and Development (OECD) on November the 6th 2022. The data spans a period of 60 years, between 1960 and 2020. After matching this data with clinical endpoints, we ended up using the suicide data for the period between 1979 and 2016. We chose global suicide rate as our main measure as it mirrored mood and mental health status on a global level. However, the study protocol also leveraged homicide and violent crime rates as alternative metrics to replicate the main findings (see **Supplement Tables S2-3, Figures S4-5**). As a result of data merging, 93 unpublished studies had to be excluded from the analysis due to absent information on publication year preventing matching with the socionomic metrics.

Endpoints

The primary study endpoints were proportion of responders (≥ 50% reduction of the total score on a standardized observer-rating scale for depression) and remitters, relative to a total number of randomized patients in a placebo group. The final dataset included a total of 429 studies, of which 216 and 398 included information on responders, 205 and 381 on remitters in placebo and active groups, correspondingly. Data on dropouts was available for 205 and 378 in active and placebo groups, respectively. Total number of subjects was reported in all but one trials.

Analysis

Data analysis leveraged linear and non-linear methods to estimate the effect-sizes, Pearson correlation and mutual information criteria, respectively. The first step of the analysis was focused on the whole dataset estimating magnitude of the relationships between the study outcomes and global suicide rates (averaging corresponding metrics across 46 countries reported in the OECD database). Following this, the discovered associations were further tested in linear models adjusting for effects of time (publication year), initial depression severity and study size (total number of included subjects). The afore-mentioned steps were then repeated on

a subset of studies conducted in North America matching the study outcomes with suicide rates of the United States and of 37 other countries available in the dataset as well as with suicide rates of 15 countries with previously researched cultural dissimilarities (20). The effect of socionomic distance on the discovered associations (Pearson r and mutual information) was further quantified leveraging the same (linear and non-linear) criteria. The main analyses were preregistered at Open Science Foundation website (http://bit.ly/3EZHMse).

We also explored possible effects of socionomic temporal distance. To do that, we evaluated associations with time-lagged Pearson correlation for the full data-set with an expectation that earlier suicide rates would be more strongly predictive of the trial outcomes (overlapping with the period of approximately when the studies were conducted) than the later ones.

Results

Primary analyses

The primary analyses confirmed hypothesized associations between changes in suicide rates and outcomes of clinical trials. The effects were present in the whole dataset, as well as in a subset of studies conducted in North America.

Specifically, in the periods of higher suicide rates proportion of responders and remitters (primary study endpoints) was significantly smaller for both placebo and active treatment (Responders $_{Placebo}$ r = -0.38 (95% C.I.: -0.49, -0.26), P < 0.001; Remitters $_{Placebo}$ r = -0.42 (95% C.I.: -0.53, -0.30), P < 0.001; Responders $_{Active}$ r = -0.09 (95% C.I.: -0.19, 0.004), P = 0.06; Remitters $_{Active}$ r = -0.12 (95% C.I.: -0.22, -0.02), P = 0.02) and the opposite was observed for study dropouts (Dropouts $_{Placebo}$ r = 0.56 (95% C.I.: 0.45, 0.64), P < 0.001; Dropouts $_{Active}$ r = 0.32 (95% C.I.: 0.22, 0.40), P < 0.001), Fig. 2. The effect sizes were medium to large for the placebo group correlations but low to medium for the active group. Corresponding effect-sizes estimated with mutual information criterion are reported in the Supplement (**Supplement Figure S8**). Of note, since substantial deviations from normality was observed for distributions of dropouts (**Supplement Figure S2**), we also replicated the results leveraging Spearman rank correlation coefficient (**Supplement Table S6**).

Importantly, whilst being present in both placebo and active groups, this effect was particularly strong in placebo arms, as also demonstrated by significant group-by-metric interaction effects on study outcomes (Responders $_{Suicides\ X\ Group}$: β_{std} = -0.013 ± 0.005, T=-2.636, P = 0.009; Remitters $_{Suicides\ X\ Group}$: β_{std} = -0.01 ± 0.005, T=-2.029, P = 0.043; Dropouts $_{Suicides\ X\ Group}$: β_{std} = 0.02 ± 0.005, T = 4.453, P < 0.001; See Table 1). As expected, the opposite was observed for dropouts due to side-effects with larger impact seen in the active group, which was also assessed in exploratory analyses (Table 1, Fig. 3). It is worth noting, however, that significant effects on side effects-related dropouts were also observed for the placebo arm.

Repeating the analysis for a subset of North American studies matched with suicide rates of USA and Canada yielded equivalent effect-sizes to the ones of the primary analysis conducted on the full data set (Responders $_{Placebo}$ r = -0.49 (95% C.I.: -0.67, -0.27), P < 0.001, Responders $_{Active}$ r = -0.02 (95% C.I.: -0.20, 0.24), P = 0.88; Remitters $_{Placebo}$ r = -0.51 (95% C.I.: -0.69, -0.27), P < 0.001, Remitters $_{Active}$ r = -0.06 (95% C.I.: -0.29, 0.18), P = 0.61; Dropouts $_{Placebo}$ r = 0.39 (95% C.I.: 0.13, 0.60), P = 0.004; Dropouts $_{Active}$ r = 0.11 (95% C.I.: -0.12, 0.33), P = 0.36). See **Supplement Figure S3** for scatter plots and the investigated interactions effects replicated in the North American subsample.

Bias Correction

It is worth noting that previous studies have identified a number of important biases in placebo effects, such as sample size and publication year. They were replicated in the present study (Responders ~ N $_{Placebo}$ r = 0.33 (95% C.I.: 0.21, 0.45), P < 0.001; Responders ~ Year $_{Placebo}$ r = -0.44 (95% C.I.: 0.33, 0.54), P < 0.001; Remitters ~ N $_{Placebo}$ r = 0.30 (95% C.I.: 0.17, 0.42), P < 0.001; Remitters ~ Year $_{Placebo}$ r = 0.45 (95% C.I.: 0.34, 0.56), P < 0.001).

Recognizing importance of Furukawa's observations, questioning overall increase of placebo effects over time (1), we performed an extra analysis of this effect in the placebo group introducing the key confounds (trial duration and proportion of multicenter studies) and replicated their findings showing that the effect of publication year was no longer significant after adjusting the results for sample size, average trial duration and proportion of multicenter studies on a given year (Responders ~ Year $_{Placebo}$: β_{std} = -0.05 ±

0.03, T = 1.89, P = 0.06; Remitters ~ Year $_{Placebo}$: β_{std} = -0.01 ± 0.03, T = 0.36, P = 0.72). In line with Furukawa's findings, proportion of multicenter studies was a consistent contributor to this association (Responders ~ Number of Centers $_{Placebo}$: β_{std} = 0.029 ± 0.014, T = 1.89, P = 0.04; Remitters ~ Number of Centers $_{Placebo}$: β_{std} = 0.04 ± 0.013, T = 3.20, P = 0.002).

Sensitivity analyses and secondary analyses

We then performed adjustment for sample size, publication year and standardized (z-scored) baseline severity of depression confirming the differential effects of social mood in placebo and active study arms (Table 1). This was also shown for the truncated North-American data set (See **Supplement Table S1**). Evaluating robustness of the main findings, we also introduced trial duration and proportion of multicenter studies as extra confounds from Furukawa's analysis. Despite the fact that the data was only available for the years 1978–2015, both factors were strongly associated with the primary study outcomes. However, introducing these two extra confounds had very little influence on the main findings confirming stability of the identified differential effects of suicide rates on treatment outcomes in placebo and active study arms.

We also repeated the main analyses steps for alternative metrics and identified a similar pattern of associations for rates of *homicides* (Responders $_{Placebo}$ r = -0.26 (95% C.I.: -0.39, -0.12), P = 0.002; Remitters $_{Placebo}$ r = -0.31 (95% C.I.: -0.43, -0.16), P < 0.001; Responders $_{Active}$ r = -0.09 (95% C.I.: -0.19, 0.02), P = 0.11; Remitters $_{Active}$ r = -0.13 (95% C.I.: -0.24, -0.03), P = 0.02; Dropouts $_{Placebo}$ r = 0.57 (95% C.I.: 0.46, 0.66), P < 0.001; Dropouts $_{Active}$ r = 0.28 (95% C.I.: 0.18, 0.38), P < 0.001) and *violent crime* (Responders $_{Placebo}$ r = -0.37 (95% C.I.: -0.48, -0.24), P < 0.001; Remitters $_{Placebo}$ r = -0.43 (95% C.I.: -0.54, -0.30), P < 0.001; Responders $_{Active}$ r = -0.13 (95% C.I.: -0.22, 0.025), P = 0.01; Remitters $_{Active}$ r = -0.14 (95% C.I.: -0.24, -0.03), P = 0.009; Dropouts $_{Placebo}$ r = 0.60 (95% C.I.: 0.50, 0.68), P < 0.001; Dropouts $_{Active}$ r = 0.33 (95% C.I.: 0.23, 0.42), P < 0.001). Similar, but slightly weaker pattern was observed for *homicides* and *violent crime* when adjusting for publication year, sample size and baseline depression severity (See **Supplement Tables S2-3, Figures S4-5**).

While the first half period of our measurements of suicides displayed a relatively stable phase in relation to number of suicides, the second half period displayed a linear decrease in suicides (**Supplement Figure S1**). In order to test that our results were not purely driven by the linear effect we performed a separate analysis after a median split of the studied period. This analysis suggested that the main socionomic effects remained stable in each of the two periods (**Supplement Tables S4-5**). However, the interactions effects between placebo and active groups, while having the same direction, were no longer significant, possibly due to smaller magnitude of changes in social mood within the studied phases. Notably, when analyzing only North American data (RCTs and suicide rates) similar results emerged, although suicide trend has been rising since 2000 in the US in contrast to the decline on a world-wide level (**Supplement Figure S10**).

[Insert Table 1 here]

Analyses of socionomic and temporal distance

By matching outcomes of clinical trials conducted in North America with suicide rates of the United States and of 37 other countries available in the dataset we found that more dissimilar suicide patterns also show a less stable effect (that was even reversed for the most distant countries, Fig. 4a). This was further confirmed in a follow-up analysis investigating relationships between the magnitude of the effect sizes and cultural distances independently assessed by Liu et al., 2018 (20) (**Supplement Figure S6**).

To explore the effects of temporal distance, we evaluated associations with time-lagged Pearson correlation for the full dataset. We found that outcomes of clinical trials exhibit stronger correlations with earlier suicide rates peaking approximately 8–9 years before the publication date and weaker correlations with later suicide rates (Fig. 4b, see **Supplement Figure S7** for the results with mutual information criterion).

Discussion

Accumulating evidence suggests that societal changes exhibit strong impact on wellbeing both on an individual and a population level (11–15, 18, 19). The present study addressed the question of how placebo and antidepressant treatment effects in randomized controlled trials are dependent on such global socionomic sentiment, here indexed by national level suicide rates.

A principal finding showed that the outcomes are highly related to socionomic context, aka social mood, in the placebo group. Specifically, in periods of higher rates of suicides, as well as violent crimes and homicides, the proportion of responders and remitters tends to be significantly smaller and the opposite effects are seen for study dropouts. Such effects are also seen in the active treatment arms but to a smaller degree. This demonstrates that maximum difference between placebo and active antidepressant treatment is highest during periods of negative social mood. The findings have major clinical implications as the difference in primary outcomes between active and placebo arms was more than two times larger between the best and worst socionomic periods and even more substantial for dropouts. This substantial variation in the effectiveness of the drug over time suggests that it is important to consider the influence of contextual factors on antidepressant treatment and may help to explain the inconsistencies in the results of previous clinical trials.

It is important to note that while the suicide rate remained relatively stable during the first half of the study period, it was steadily decreasing during the second half. Our analysis of these two phases revealed that the relationships between the studied outcomes were similar in both phases. However, the main effects of social mood on study outcomes were substantially smaller within each of the two phases and the interactions with the study arms were no longer significant. This suggests that the greatest effect of social mood on clinical outcomes occurs during transitions between the two states. This is consistent with previous findings that identified the largest effects of social mood on well-being during socioeconomic phase transitions (15). Of note, using only data from the United States (suicide rates and clinical outcomes) generated a similar result as world data even though suicide rates have been steadily been increasing since 2000, in contrast to the global data.

When only considering a subset of North American studies, weaker effects on these outcomes were observed for social mood of countries that are more distant from the United States. A similar pattern of associations was shown for temporal distance, i.e. the effects were larger for earlier suicide rates (with a peak of eight to nine years before study publication) and weaker for the data sampled later in time. This result preliminary suggests that a maximum impact may occur during recruitment and trial execution periods.

The finding that the placebo effect decreased more than the antidepressant effect in the worst socionomic periods, mirrors previously reported interaction with depression severity differently affecting outcome of placebo and active drug (where the placebo effect is lowest and, thus, the specific effect is largest, in the most severe depressions) (3). Importantly, we find that socionomic sentiment exhibits independent contribution to the study outcomes, as adjusting for baseline depression severity did not eliminate the effects reported in the present study. Our main results also withstood correction for a number of important confounds, including publication year bias previously explored in-depth by Furukawa et al. who challenged the notion of a linear increase in placebo effects over time (1). This bias was present in our sample too. However, in line with Furukawa's findings, it was no longer significant after adjusting for trial duration and proportion of multicenter studies. Introducing these two extra confounds into the model had very little influence on the main interaction term confirming robustness of differential effects of social mood on placebo and active study arms.

It is worth noting, that previous research has identified amplifying effects of environmental conditions on treatment outcomes (21), which is in line with the main effect of socionomic sentiment seen in the present study in both groups. Taken together, these observations highlight the importance of contextual and environmental factors for pharmacological treatment outcomes. Of relevance for future studies, these effects may even be larger for outcomes of psychotherapeutic interventions, combinations of psychotherapy with antidepressant treatment (22), or other emerging approaches, such as drug-assisted psychedelic therapy (23, 24), in which the key importance of setting and environment is well-known (25).

The placebo response has been suggested to be dependent of an active information processing mechanism relying on expectations (26–30).The discovered effect of the socionomic sentiment may reflect an overall influence of the environment including the interactions with health care professionals on patients' attitudes and expectations, thereby modifying perceived efficacy of treatments (7). Another plausible interpretation can be that "better times" provide better environmental means for spontaneous remissions instead of affecting patients' treatment expectations.

Some limitations should be taken into account when interpreting the results. We could not effectively control for all different antidepressants given in different studies, since the socionomic data was sampled annually and multiple active substances could be tested in the same years. Also, limited information on study details, makes it impossible to disentangle placebo effects and

spontaneous remissions (31, 32). Another limitation pertains to the characteristics used socionomic metric where it is known that reporting rates (e.g. of suicides) depends on local culture and it is expected that some countries underreport. As such under-reporting remain stable over time the influence on our findings is considered negligible. The present study did not assess possible within-country changes in the suicide data collection approaches that may be happening over the course of the investigated period. This is particularly relevant for the analysis of temporal distances, which must be interpreted with caution. Finally, we did not explore a wide variety of other socionomic metrics, such as housing prices, unemployment rates and behavior of capital markets used in previous studies (15). As these variables exhibit strong linear trend when sampled over long periods and are not as directly implicated to the clinical outcomes investigated in the present study, we deemed them as less relevant for addressing the research question in focus. Finally, the present study did not address the effects of media sentiment (33, 34) around the investigated treatments, which is known to have a marked effect on patients' opinions and expectations (35). Future studies in this important vein of research may help to prepare the public and healthcare decision-makers to mitigate the potential consequences of disbalanced attitudes toward novel treatment approaches (36).

The results also revealed that regular dropouts and those who dropped out of the studies due to side effects were differentially impacted by suicide rates in the placebo and active treatment groups. This suggests that socionomic sentiment may interact with a patient's adherence to treatment. However, a caution is advised when interpreting this particular observation, since dosing variability and effects of different active treatments may constitute a confounding effect, which was not analyzed in the present study. Finally, since a significant increase in dropouts due to side-effects was also observed in the placebo arms during periods of higher suicide rates, the results suggest a possible augmentation of the nocebo effect accompanying worsening of the social mood. All of these explanations, support the importance of socionomic sentiment for treatment outcomes.

Taken together, our results suggest that global societal wellbeing is strongly associated with outcomes of antidepressant clinical trials with particularly marked effects seen in placebo arms. The findings suggest that socionomic sentiment must therefore be taken into account when evaluating efficacy of interventions attempting to impact mental health outcomes.

Declarations

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Data sharing statement:

The study used publicly available meta-analysis dataset by Cipriani et al. (6), which was made publicly available by the authors at https://www.thelancet.com. The socionomic outcome in the form of annual suicide rates was accessed from The Organization for Economic Co-operation and Development (OECD) on November the 6th 2022 (https://www.oecd.org).

Ethics statement:

The study adhered to the tenets of the Declaration of Helsinki, 2013.

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Tables

Table 1

Standardized estimates for the investigated relationships between global suicide rates and outcomes of clinical trials. Primary study endpoints are highlighted in light grey, main contrasts-of-interest are highlighted in bold. ° - P < 0.1, * - P < 0.05; ** - P < 0.01; *** - P < 0.001; BL Depression – baseline level of depression; Length – Mean length of trials; MC – proportion of multicenter studies, Negative group effects represent smaller scores observed in placebo groups compared to active treatment arms.

	Suicides	Group	Interaction	Year	N	BL Depression	Length	MC
Minimal Model								
Responders	**β=-0.023 ± 0.005, T=-4.487*** **	β=-0.094 ± 0.005, T=-18.554***	**β=-0.013 ± 0.005, T=-2.636** **	–	–	–	–	–
Remitters	**β=-0.025 ± 0.005, T=-4.787*** **	β=-0.07 ± 0.005, T=-13.52***	**β=-0.01 ± 0.005, T=-2.029***	–	–	–	–	–
Dropouts	β = 0.055 ± 0.005, T = 10.951***	β = 0.028 ± 0.005, T = 5.481***	β = 0.022 ± 0.005, T = 4.453***	–	–	–	–	–
SEdropouts	β = 0.02 ± 0.002, T = 7.963***	β=-0.026 ± 0.002, T=-10.461***	β=-0.009 ± 0.002, T=-3.833***	–	–	–	–	–
Adjusted Model 1								
Responders	**β=-0.004 ± 0.015, T=-0.234**	β=-0.091 ± 0.005, T=-17.738***	**β=-0.014 ± 0.005, T=-2.862** **	β = 0.014 ± 0.015, T = 0.927	β = 0.004 ± 0.006, T = 0.679	β = 0.017 ± 0.005, T = 3.248**	–	–
Remitters	**β=-0.031 ± 0.018, T=-1.745°**	β=-0.071 ± 0.005, T=-13.084***	**β=-0.011 ± 0.005, T=-2.018***	β=-0.005 ± 0.018, T=-0.263	β=-0.003 ± 0.006, T=-0.441	β=-0.008 ± 0.006, T=-1.471	–	–
Dropouts	β = 0.052 ± 0.016, T = 3.358***	β = 0.023 ± 0.005, T = 4.373***	β = 0.022 ± 0.005, T = 4.309***	β = 0.003 ± 0.016, T = 0.186	β=-0.013 ± 0.006, T=-2.168*	β=-0.021 ± 0.005, T=-4.052***	–	–
SEdropouts	β = 0.011 ± 0.007, T = 1.465	β=-0.024 ± 0.002, T=-10.578***	β=-0.008 ± 0.002, T=-3.402***	β=-0.006 ± 0.007, T=-0.775	β=-0.002 ± 0.003, T=-0.861	β=-0.001 ± 0.002, T=-0.437	–	–
Adjusted Model 2								
Responders	**β = 0.02 ± 0.02, T = 0.999**	β=-0.089 ± 0.005, T=-17.854***	**β=-0.016 ± 0.005, T=-3.197** **	β = 0.006 ± 0.023, T = 0.276	β = 0.002 ± 0.006, T = 0.415	β = 0.018 ± 0.005, T = 3.627***	β=-0.023 ± 0.007, T=-3.363***	β = 0.029 ± 0.01, T = 2.864**
Remitters	**β=-0.013 ± 0.024, T=-0.52**	β=-0.069 ± 0.005, T=-13.084***	**β=-0.012 ± 0.005, T=-2.385***	β=-0.027 ± 0.028, T=-0.971	β=-0.005 ± 0.006, T=-0.839	β=-0.007 ± 0.005, T=-1.335	β=-0.023 ± 0.007, T=-3.069**	β = 0.041 ± 0.011, T = 3.652***
Dropouts	β = 0.045 ± 0.021, T = 2.151*	β = 0.022 ± 0.005, T = 4.239***	β = 0.023 ± 0.005, T = 4.505***	β = 0.014 ± 0.024, T = 0.581	β=-0.012 ± 0.006, T=-1.947°	β=-0.022 ± 0.005, T=-4.214***	β = 0.01 ± 0.007, T = 1.487	β=-0.018 ± 0.01, T=-1.759°
SEdropouts	β = 0.015 ± 0.01, T = 1.535	β=-0.025 ± 0.002, T=-10.642***	β=-0.007 ± 0.002, T=-3.295**	β = 0.004 ± 0.011, T = 0.341	β=-0.002 ± 0.003, T=-0.819	β=-0.001 ± 0.002, T=-0.454	β=-0.001 ± 0.003, T=-0.168	β=-0.006 ± 0.005, T=-1.376

Figures

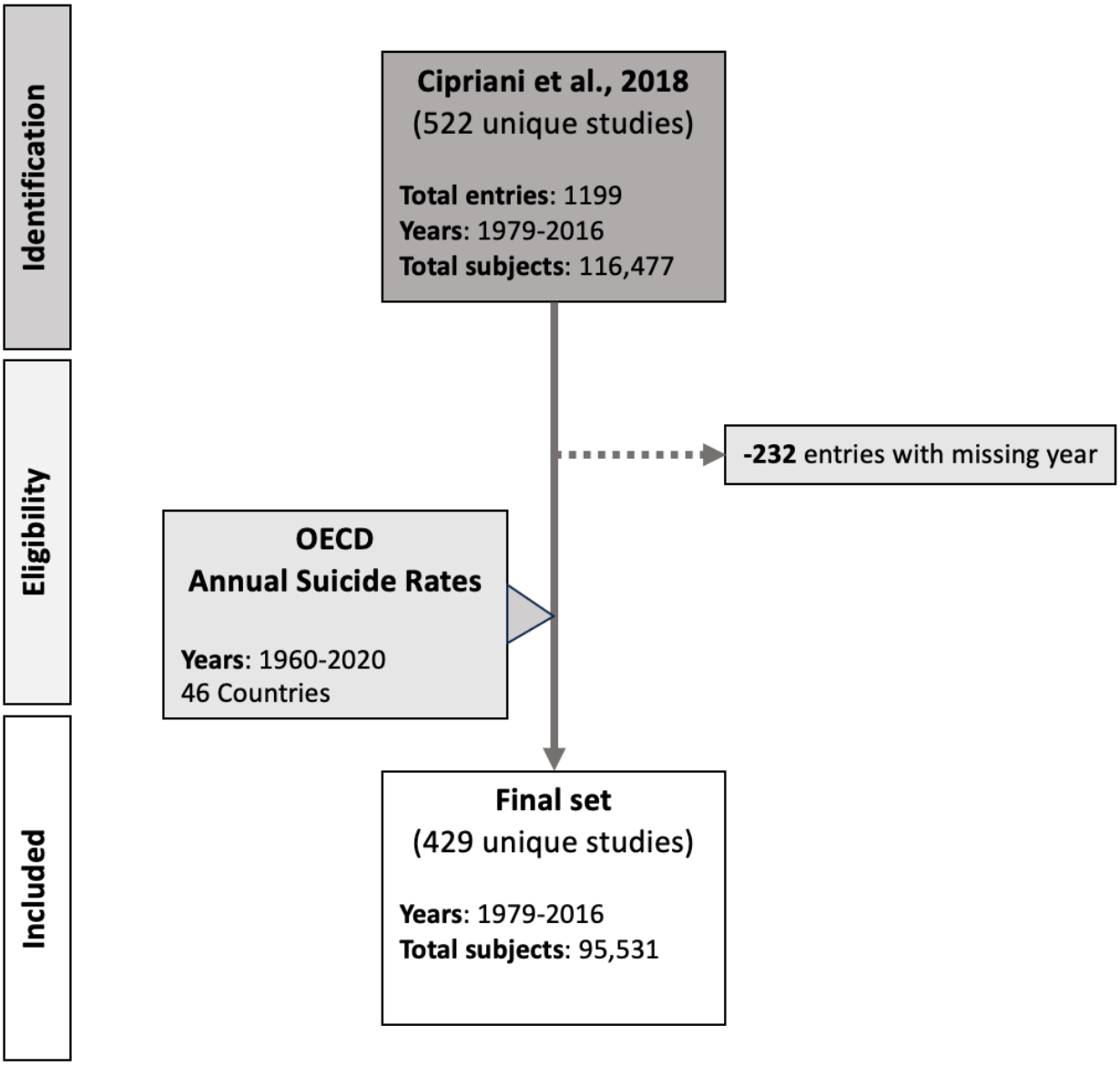

Figure 1

Study flow diagram. From a total dataset of 522 trials (1199 entries) included in Cipriani et al. 2018 (6), 232 entries lacking a publication year were removed yielding a final dataset of 429 unique trials. This data was matched with global suicide rates accessed from The Organization for Economic Co-operation and Development (OECD).

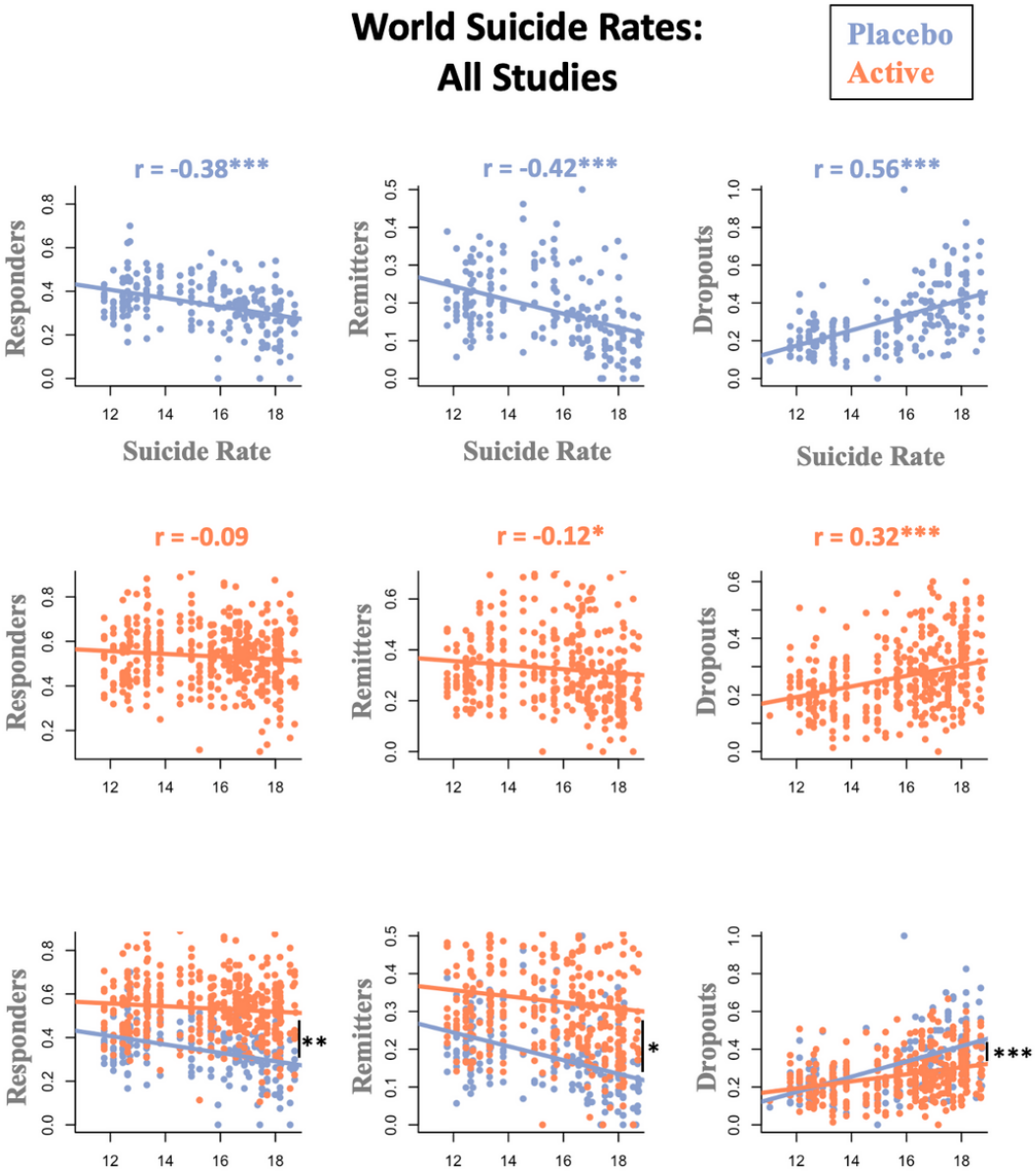

Figure 2

Scatter plots representing relationships between worldwide suicide rates and outcomes of clinical trials in placebo and active treatment arms (whole sample).

*** - P<0.001, ** - P<0.01, * - P<0.05; asterisks next to vertical lines represent significance of interaction terms.

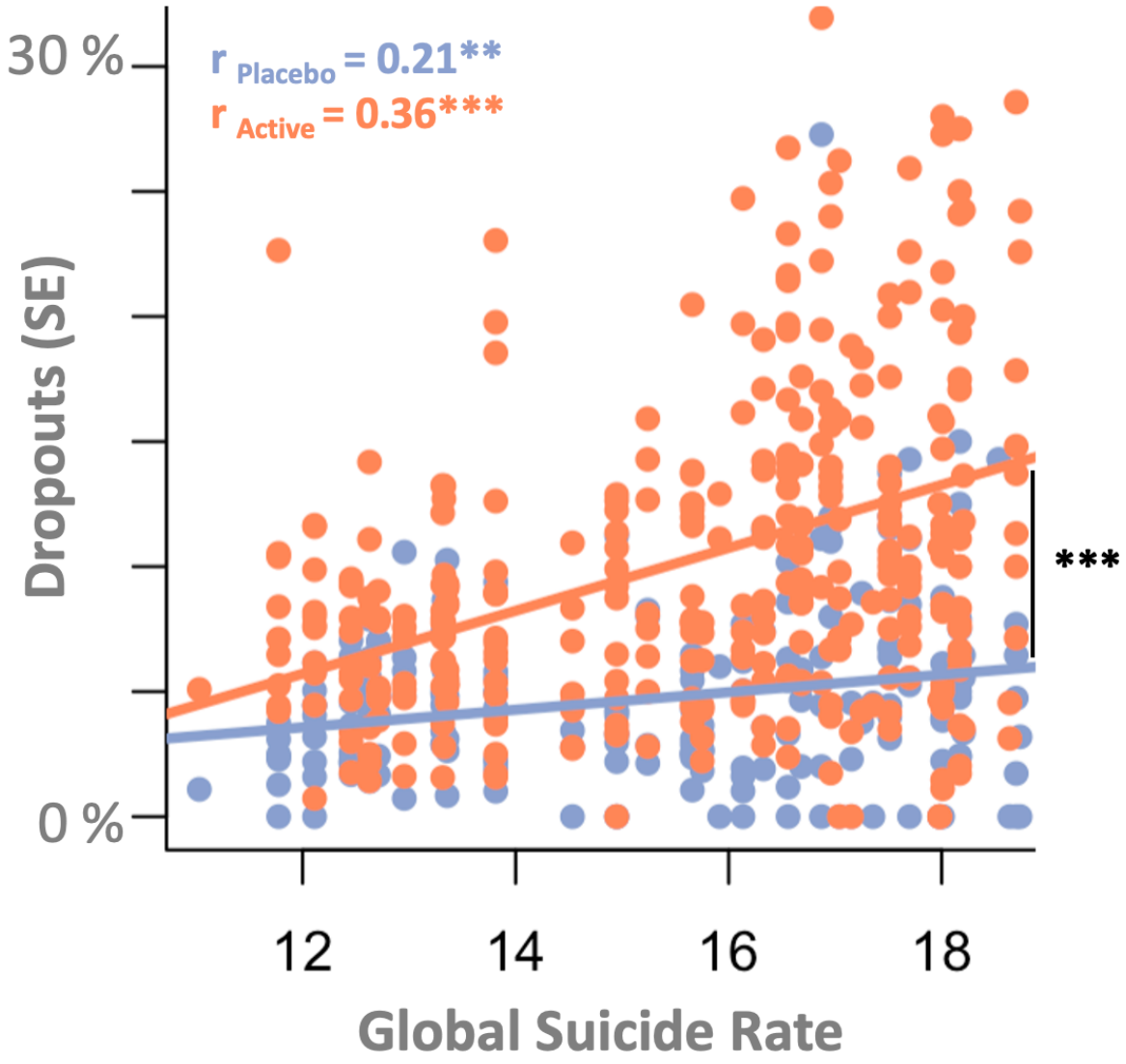

Figure 3

Scatter plots representing relationships between worldwide suicide rates and dropouts due to side-effects (SE) of clinical trials in placebo and active treatment arms (whole sample). *** - P<0.001, ** - P<0.01; asterisk next to vertical lines represents significance of the interaction term.

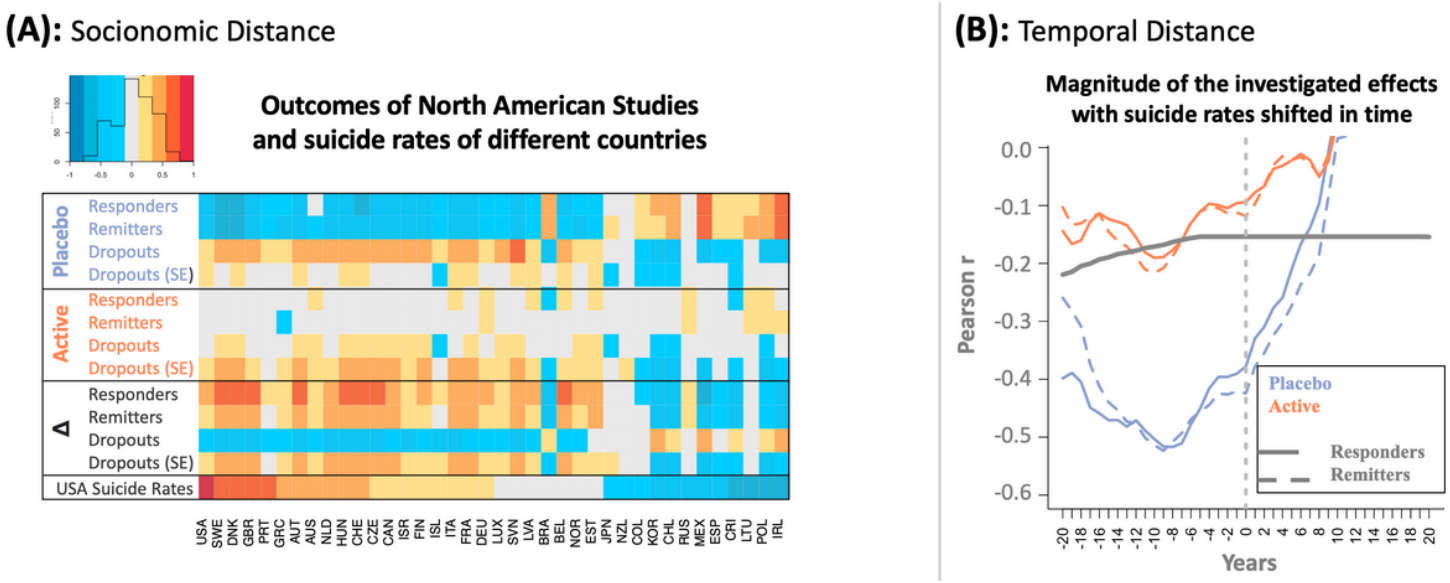

Figure 4

Impact of socionomic distance and temporal distances on the investigated relationships between the study outcomes and the socionomic sentiment. **Panel A, Socionomic Distance:** The analysis revealed clustering of the effects in relation to sociocultural differences, which were further explored in **Supplement Figure S6**.**Panel B, Temporal Distance:** main clinical outcomes (proportion of responders and remitters) exhibit stronger correlations with earlier suicide rates peaking approximately 8 years before the publication date with substantially larger effects observed in placebo groups. The opposite is seen for later suicide rates.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- METASupplement202310XXX03anonymised.pdf