The association between personality traits and placebo effects: A preregistered systematic review and meta-analysis

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Abstract

Placebo effects are ubiquitous yet highly variable between individuals, and therefore strongly impact clinical trial outcomes. It is unclear whether dispositional psychological traits influence responsiveness to placebo. This preregistered meta-analysis and systematic review synthesized the literature investigating the association between personality traits and placebo effects. Based on 19 studies with 712 participants, we performed formal meta-analyses for 10 different personality traits. We did not find evidence of associations between any of these traits and magnitude of placebo effects, which was supported by equivalence tests. Furthermore, we did not find evidence for moderating factors such as placebo manipulation type (Conditioning, non-conditioning) or condition (pain, non-pain). However, the current synthesis was not statistically powered for full inquiry into potential conditional or interactive associations between personality and situational variables. These findings challenge the notion that personality influences responsiveness to placebos and contradict its utility for identifying placebo "responders" and "non-responders".

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Introduction

The placebo effect – i.e. the therapeutic improvement following the administration of an inert treatment – is commonly used as a scientific model for investigating how expectations, cognition, and affect can influence sensory experiences and symptoms (Atlas, 2021). On the other hand, the large variability in individual placebo effects cause problems for clinical trials, which aim to assess the specific effects of drugs or interventions (Walach et al., 2005). The idea that individual responsiveness to placebo effects can be explained, to some extent, by stable psychological factors such as personality, has a long history (S. Fisher & Fisher, 1963; Jellinek, 1946; Lasagna et al., 1954), and is widespread both in research and among clinical trialists today (Frisaldi et al., 2018; Pecina et al., 2013; Schedlowski et al., 2015; Vachon-Presseau et al., 2018; Weimer et al., 2015, p. 2). Personality traits can be defined as "consistent patterns of thoughts, feelings, and actions across developmental periods and contexts"(McCrae & Costa, 2003), and are thought to play a key role in various clinical contexts, especially in psychiatry and clinical psychology. While placebo effects have been linked to a range of different personality traits (Darragh et al., 2014; Geers et al., 2010; Schweinhardt et al., 2009), some researchers have questioned the existence of a "placebo personality" and even the notion of individual consistency in placebo responsiveness (Buckalew et al., 1981; Kaptchuk et al., 2008; Shapiro et al., 1973, 1975). Despite a wealth of studies of different candidate traits associated with a "placebo personality" (Jakšić et al., 2013; Kern et al., 2020), there is currently no meta-analytic evidence for whether personality traits influence placebo effects.

In clinical trials, especially in the fields of pain, depression, and mood disorders, high placebo responses are often seen as essentially raising the bar for drug arms to "beat" the placebo response (Enck et al., 2013), contributing to many clinical trials failing to find significant effects. To address this issue, clinical trials have employed various methods to reduce, or control for, placebo response rate, e.g. trying to identify (and sometimes exclude (Bosman et al., 2021; Scott et al., 2021)) people who would respond favorably to placebos (Jellinek, 1946; Trivedi et al., 2018). Following the emergence of modern randomized controlled trials in the 1940s-50s, it was soon suggested that individuals may show a consistent tendency to respond ("placebo reactor") or not respond ("placebo non-reactor") positively to placebos (Beecher et al., 1953), and that this tendency may be explained by personality traits. An early influential study, using Rorschach interviews in patients receiving treatment for post-operative pain, found that consistent "placebo reactors" were more frequently "talkative, churchgoing, anxious, self-centered, interoceptive, and emotionally labile", compared to non-reactors (Lasagna et al., 1954). They speculated that such individuals may be "more dependent on outside stimulation than on their own mental processes" in order to relieve anxiety and tension, which in turn made them respond positively to placebo treatment. Subsequent studies reported that placebo reactors scored higher on "social acquiescence", or social desirability, which are related concepts for the tendency to conform to, or agree with, others' suggestions irrespective of the content (S. Fisher & Fisher, 1963; McNair et al., 1979). Along similar lines, hypnotic suggestibility (Leigh et al., 2003) and agreeableness (Kelley et al., 2009) have more recently been linked to higher placebo responding. Building on these concepts, recent theoretical frameworks have proposed that "inward" and "outward" orientation may predispose individuals to respond to placebos depending on context (Darragh et al., 2015). Several additional modern hypotheses on the "placebo personality" have been pursued.

First, positive expectations of a beneficial therapeutic outcome is commonly considered a key contextual mechanism of placebo effects (Kirsch, 1985; Schwarz et al., 2016) . Correspondingly, dispositional optimism has been proposed to promote placebo effects by increasing the expectancy of a positive therapeutic outcome (Darragh et al., 2015; Geers et al., 2005, 2007, 2010; Kern et al., 2020; Scheier & Carver, 1992). Conversely, more pessimistic people may react more saliently to information about adverse outcomes and side effects, which in turn may contribute to nocebo effects. Trait anxiety, which is sometimes negatively associated with optimism (Scheier et al., 1994), and related to negative expectancy bias (Cabeleira et al., 2014) has been suggested as a negative predictor of placebo responsiveness (Broelz et al., 2019; Horing et al., 2014; Morton et al., 2009; Pecina et al., 2013). Similarly, neuroticism (Pecina et

al., 2013), pain catastrophizing(Sullivan et al., 2008), fear of pain (Corsi & Colloca, 2017; Lyby et al., 2010) have been linked to placebo effects as a negative predictor.

Second, in line with previous findings suggesting that placebo improvement is underpinned by brain circuitry supporting reward and valuation mechanisms (Ashar et al., 2017; De la Fuente-Fernández et al., 2001; Ellingsen et al., 2013; Fields, 2004; Lidstone et al., 2005; Mayberg et al., 2002; Oken et al., 2008; Petrovic et al., 2002; Scott et al., 2007, 2008), another central hypothesis is that traits related to behavioral activation and reward responsiveness may be a positive predictor of placebo responsivity (De Pascalis & Scacchia, 2019; Schweinhardt et al., 2009). Conversely, behavioral inhibition has been linked to anxiety (Carver & White, 1994), and thus may be negatively associated with placebo improvement (Broelz et al., 2019).

Finally, since placebo-related improvement is influenced by the social context, such as qualities of a patient-clinician interaction (Ellingsen et al., 2020; Kelley et al., 2009) or by observing what happens to others who receive the same treatment (Colloca & Benedetti, 2009; Schenk & Colloca, 2020), traits related to dispositional empathy have been hypothesized to promote placebo effects(Davis, 1983). A general hypothesis is that an individual who scores high on empathy, and thus better internalizes others' experience, may be more likely to form a positive expectation after observing other participants' symptom improvement (Colloca & Benedetti, 2009; Hunter et al., 2014; Valentini et al., 2014).

Although the role of personality in placebo effects has been subject to extensive research, no studies have yet systematically investigated the evidence for such associations using meta-analysis. We therefore aimed to systematically review and meta-analytically assess the associations between personality traits and placebo effects across different conditions. For each identified personality trait, we synthesized correlation coefficients between individual trait scores and magnitude of placebo effect. Next, we tested if factors such as condition (pain, non-pain), placebo manipulation type (conditioning, non-conditioning), and placebo administration method (drug, non-drug) could explain heterogeneity between studies. Finally, we investigated the degree to which the results were influenced by outliers, publication year, study quality, or the inclusion of unpublished studies.

Results
Study selection and identified studies

We performed a systematic database search and identified 2,211 records in total (see Methods for full details). After removing duplicates and non-primary studies (e.g., re-analysis of existing data, conference abstracts, books, and protocols for pilot studies), 1226 reports were sought for retrieval of full text. 13 records were additionally identified via citation searching and suggestions from study authors. 1114 reports were retrieved and assessed for eligibility, and a total of 30 experimental studies with 294 effect measures were identified for this review. These studies included a total of 1310 participants (mean±SD age: 35.41±24.52). An overview of the study selection process is presented in **Figure 1**.

A total of 24 studies assessed pain outcomes induced by pressure (Ellingsen et al., 2020; Whalley et al., 2008), heat stimulation (Corsi & Colloca, 2017; Eippert et al., 2009; Ellingsen et al., 2014; Geisler et al., 2020; Huber et al., 2013; Kessner et al., 2014; Meyer et al., 2015; Ruscheweyh et al., 2014; Schweinhardt et al., 2009; Stein et al., 2012; Weimer et al., 2019), electric stimulation (Colloca et al., 2010; Colloca & Benedetti, 2009; Hunter et al., 2014; Meyer et al., 2019; Rosen et al., 2017; Tang et al., 2019), laser (Valentini et al., 2014), saline injection (Lund et al., 2015; Pecina et al., 2013), and cold stimulation (De Pascalis & Scacchia, 2017, 2019). Seven studies used non-pain outcomes, including tactile perception induced by electric stimulation (Colloca et al., 2010), brush touch (Ellingsen et al., 2014; Ellingsen et al., 2013), warm touch (Ellingsen et al., 2013), stress (Darragh et al., 2014), experience of extraordinary events (Maij & van Elk, 2018), exercise performance (Saunders et al., 2019), and disgust (Zorjan et al., 2019). Expectations of positive therapeutic effects were induced by verbal suggestion (Colloca & Benedetti, 2009; Darragh et al., 2014; De Pascalis & Scacchia, 2017, 2019; Eippert et al., 2009; Ellingsen et al., 2014; Ellingsen et al., 2013; Hunter et al., 2014; Lund et al., 2015; Meyer et al., 2015, 2019; Pecina et al., 2013; Rosen et al., 2017; Ruscheweyh et al., 2014; Saunders et al., 2019; Stein et al., 2012; Whalley et al., 2008; Zorjan et al., 2019), social observation (Colloca & Benedetti, 2009; Ellingsen et al., 2020; Hunter et al., 2014; Maij & van

Elk, 2018), and conditioning (Colloca et al., 2010; Colloca & Benedetti, 2009; Corsi & Colloca, 2017; Geisler et al., 2020; Huber et al., 2013; Hunter et al., 2014; Kessner et al., 2014; Schweinhardt et al., 2009; Tang et al., 2019; Valentini et al., 2014; Weimer et al., 2019). Eighteen studies used a medicine/drug-based placebo, including topical cream (De Pascalis & Scacchia, 2017, 2019; Eippert et al., 2009; Geisler et al., 2020; Ruscheweyh et al., 2014; Schweinhardt et al., 2009; Stein et al., 2012; Weimer et al., 2019; Whalley et al., 2008), pill or capsule (Saunders et al., 2019; Zorjan et al., 2019), inhalation of gas (Meyer et al., 2019), nasal spray (Darragh et al., 2014; Ellingsen et al., 2014; Ellingsen et al., 2013; Meyer et al., 2015), injection (Lund et al., 2015; Pecina et al., 2013). Nine studies used a non-drug approach, including placebo devices such as sham analgesic stimulation (Ellingsen et al., 2020; Rosen et al., 2017; Tang et al., 2019) and helmet (Maij & van Elk, 2018), and visual cues that were conditioned with sham analgesic stimulation (Colloca & Benedetti, 2009; Corsi & Colloca, 2017; Huber et al., 2013; Hunter et al., 2014; Valentini et al., 2014). Characteristics of identified studies are summarized in **Table S3**.

Included studies

A total of 19 studies with 171 effect sizes were included in the final synthesis. Characteristics of included studies are summarized in **Table 1**. Since some studies reported multiple effect sizes, we used Robust Variance Estimation (RVE) to control for shared variance between such effect sizes. In order to meet the statistical assumptions for RVE, we applied an *a priori* decision rule for inclusion in data synthesis for each identified personality trait. Specifically, we performed formal meta-analysis for traits in which 1) there were five or more independent observations and 2) degrees of freedom exceeded the cutoff number of effect estimates, $dfs > 4$, adjusted for small sample. Consequently, association between placebo effects and the following traits were not included in the final meta-analyses: absorption (Darragh et al., 2014; Lund et al., 2015; Maij & van Elk, 2018; Whalley et al., 2008); pain catastrophizing (Corsi & Colloca, 2017; Ellingsen et al., 2020; Geisler et al., 2020; Ruscheweyh et al., 2014; Weimer et al., 2019); anhedonia, tactile communication (Ellingsen et al., 2014; Ellingsen et al., 2013); social desirability (Eippert et al., 2009; Ellingsen et al., 2020; Geisler et al., 2020); fear of pain (Corsi & Colloca, 2017; Huber et al., 2013); agreeableness (Corsi & Colloca, 2017; Geisler et al., 2020; Pecina et al., 2013); openness (Corsi & Colloca, 2017; Geisler et al., 2020); extraversion (Corsi & Colloca, 2017; Darragh et al., 2014; Geisler et al., 2020); neuroticism (Corsi & Colloca, 2017; Darragh et al., 2014; Geisler et al., 2020; Pecina, Love, et al., 2013; Rosen et al., 2017); conscientiousness (Corsi & Colloca, 2017; Geisler et al., 2020); disgust proneness/sensitivity (Zorjan et al., 2019); interoceptive awareness (Geisler et al., 2020); suggestibility (Corsi & Colloca, 2017; De Pascalis & Scacchia, 2019; Huber et al., 2013; Lund et al., 2015); spirituality/religiosity/paranormal belief (Maij & van Elk, 2018).
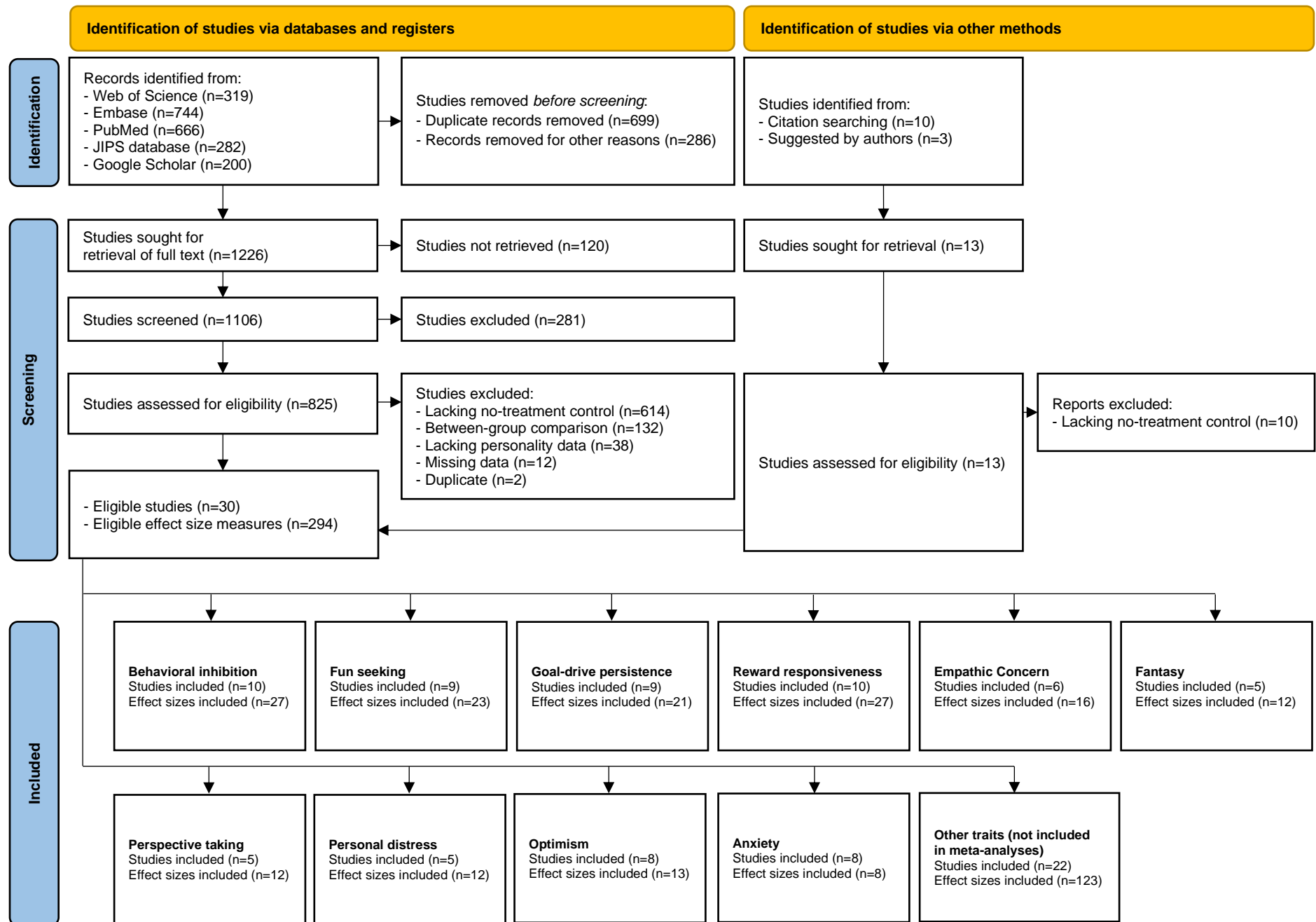
Identification of studies via databases and registers

Identification of studies via other methods

Identification

Records identified from:
- Web of Science (n=319)
- Embase (n=744)
- PubMed (n=666)
- JIPS database (n=282)
- Google Scholar (n=200)

Studies removed *before screening*:
- Duplicate records removed (n=699)
- Records removed for other reasons (n=286)

Studies identified from:
- Citation searching (n=10)
- Suggested by authors (n=3)

Screening

Studies sought for retrieval of full text (n=1226)

Studies not retrieved (n=120)

Studies sought for retrieval (n=13)

Studies screened (n=1106)

Studies excluded (n=281)

Studies assessed for eligibility (n=825)

Studies excluded:
- Lacking no-treatment control (n=614)
- Between-group comparison (n=132)
- Lacking personality data (n=38)
- Missing data (n=12)
- Duplicate (n=2)

Studies assessed for eligibility (n=13)

Reports excluded:
- Lacking no-treatment control (n=10)

- Eligible studies (n=30)
- Eligible effect size measures (n=294)

Included

Behavioral inhibition
Studies included (n=10)
Effect sizes included (n=27)

Fun seeking
Studies included (n=9)
Effect sizes included (n=23)

Goal-drive persistence
Studies included (n=9)
Effect sizes included (n=21)

Reward responsiveness
Studies included (n=10)
Effect sizes included (n=27)

Empathic Concern
Studies included (n=6)
Effect sizes included (n=16)

Fantasy
Studies included (n=5)
Effect sizes included (n=12)

Perspective taking
Studies included (n=5)
Effect sizes included (n=12)

Personal distress
Studies included (n=5)
Effect sizes included (n=12)

Optimism
Studies included (n=8)
Effect sizes included (n=13)

Anxiety
Studies included (n=8)
Effect sizes included (n=8)

Other traits (not included in meta-analyses)
Studies included (n=22)
Effect sizes included (n=123)

Figure 1. Prisma 2020 flow diagram

Table 1. Characteristics of studies included in meta-analyses

Author	Status	N	Mean age	Sex (%F)	Condition	Placebo manipulation	Type of placebo	Blinding	Outcome measure	Personality trait(s)[a]
Colloca & Benedetti (2009)	Non-clinical	16	21.7	100	Pain - electrode	Social observation	Visual cue	Single	Pain intensity	Empathic concern[b], fantasy[b], perspective-taking[b], personal distress[b]
	Non-clinical	16	22.8	100	Pain - electrode	Conditioning	Visual cue	Single	Pain intensity	Empathic concern[b], fantasy[b], perspective-taking[b], personal distress[b]
	Non-clinical	16	23.5	100	Pain - electrode	Verbal suggestion	Visual cue	Single	Pain intensity	Empathic concern[b], fantasy[b], perspective-taking[b], personal distress[b]
Eippert et al. (2009)	Non-clinical	40	26.1	0	Pain - heat	Verbal suggestion	Topical cream	Double	Pain intensity	Anxiety[c]
Schweinhardt et al. (2009)	Non-clinical	22	27.4	79.5	Pain - heat	Conditioning	Topical cream	Single	Pain intensity	Behavioral inhibition[d], goal-drive persistence[e], fun seeking[d,e], reward responsiveness[e]
Stein et al. (2012)	Non-clinical	24	26.1	0	Pain - heat	Non-conditioning	Drug	Single	Pain intensity	Anxiety[c]
Ellingsen et al. (2013)	Non-clinical	28	25.5	33.3	Pain - heat, Soft touch, Warm touch	Verbal suggestion	Nasal spray	Double	Pain unpleasantness, Touch pleasantness, Warmth pleasantness	Behavioral inhibition[e], fun seeking[e], goal-drive persistence[e], reward responsiveness[e], optimism[f]
Darragh et al. (2014)	Non-clinical	29	20.5	69	Stress	Verbal suggestion	Nasal spray	Single	Self-reported stress	Empathic concern[b], fantasy[b], perspective-taking[b], personal distress[b], behavioral inhibition[e], fun seeking[e], goal-drive persistence[e], reward responsiveness[e], optimism[f]
Ellingsen et al. (2014)	Non-clinical	42	25.4	66.7	Pain - heat, soft touch	Verbal suggestion	Nasal spray	Double	Pain unpleasantness, Pain intensity, Touch pleasantness, Touch intensity	Behavioral inhibition[e], fun seeking[e], goal-drive persistence[e], reward responsiveness[e], optimism[f]
Hunter et al. (2014)	Non-clinical	15	25.2	100	Pain - electrode	Social observation via video	Visual cue	Single	Pain intensity	Empathic concern[b]
	Non-clinical	15	29.0	100	Pain - electrode	Social observation in person	Visual cue	Single	Pain intensity	Empathic concern[b]
	Non-clinical	15	23.3	100	Pain - electrode	Verbal suggestion	Visual cue	Single	Pain intensity	Empathic concern[b]
	Non-clinical	15	30.9	100	Pain - electrode	Conditioning	Visual cue	Single	Pain intensity	Empathic concern[b]
Valentini et al. (2014)	Non-clinical	27	22.8	44.4	Pain - laser	Conditioning	Visual cue	Single	Pain intensity, Pain unpleasantness	Empathic concern[b], fantasy[b], perspective-taking[b], personal distress[b], behavioral inhibition[e], fun seeking[e], goal-drive persistence[e], reward responsiveness[e]
Meyer et al. (2015) - Study 1	Non-clinical	26	25.7	46.7	Pain - heat	Verbal suggestion	Nasal spray	Single	Fear rating	Anxiety[c]

Meyer et al. (2015) - Study 2	Non-clinical	26	26	48.3	Pain - heat	Verbal suggestion	Nasal spray	Single	Fear rating	Anxiety[c]
Corsi & Colloca (2017)	Non-clinical	46	27.4	52.2	Pain - heat	Conditioning	Visual cue	Single	Pain intensity	Anxiety[c], behavioral inhibition[e, g], fun seeking[e, g], goal-drive persistence[e], reward responsiveness[e, g]
De Pascalis & Scacchia (2017)	Non-clinical	52	23.4	100	Pain - cold	Verbal suggestion	Topical cream	Single	Pain intensity, Pain distress	Behavioral inhibition[h], fun seeking[h], goal-drive persistence[h], reward responsiveness[h]
De Pascalis & Scacchia (2019)	Non-clinical	58	24.5	100	Pain - cold	Verbal suggestion	Topical cream	Single	Pain intensity, Pain distress	Behavioral inhibition[h], fun-seeking[h], goal-drive persistence[h], reward responsiveness[h]
Meyer et al. (2019)	Non-clinical	23	24.6	72.2	Pain - electrode	Verbal suggestion	Gas	Single	Fear rating	Anxiety[c]
Saunders et al. (2019)	Non-clinical	28	36	100	Exercise performance	Verbal suggestion	Capsule	Open-label	Time-to-completion	Optimism[f]
Weimer et al. (2019)	Non-clinical	78	27.4	79.5	Pain - heat	Conditioning	Topical cream	Single	Pain intensity	Sensitivity to punishment[i], sensitivity to reward[i]
Ellingsen et al. (2020)	Clinical	18	40.0	100	Pain - pressure	Social observation	Electroacupuncture	Double	Pain intensity	Empathic concern[b], fantasy[b], perspective-taking[b], personal distress[b], behavioral inhibition[e], fun seeking[e], goal-drive persistence[e], reward responsiveness[e], optimism[g]
Geisler et al. (2020)	Non-clinical	38	27.4	0	Pain - heat	Conditioning	Topical cream	Single	Pain intensity	Anxiety[c], optimism[f]

[a] Only the traits included in meta-analyses are shown. For some studies, additional traits were collected (see **Table S3** for more comprehensive details of each study); [b] Interpersonal Reactivity Index; [c] State-Trait Anxiety Inventory; [d] Temperament Character Inventory; [e] Behavioral Inhibition/Activation System; [f] Revised Life Orientation Test; [g] Tridimensional Personality Questionnaire; [h] Reinforcement Sensitivity Theory Personality Questionnaire; [i] Sensitivity to Punishment and Sensitivity to Reward Questionnaire

Associations between placebo effects and personality

Summary effect sizes for placebo effect vs. trait score correlation coefficients were calculated for each personality trait using random-effects model with RVE incorporated in order to account for dependent outcomes. Meta-analysis was performed for correlation coefficients between placebo effect and each personality trait (i.e., Behavioral inhibition, Fun seeking, Goal-drive persistence, Reward responsiveness, Empathy – Perspective-taking, Fantasy, Personal distress, Empathic concern, Optimism, and Anxiety). In summary, we found no significant correlations between placebo effects and trait score for any of the personality traits ($r<0.14$, $P>0.07$) (**Figure 2**). Full details of the meta-analyses for each personality trait are provided in **Figures S1-S10**.

A non-significant result may reflect a true underlying null effect or the lack of statistical power to detect a true effect. To formally assess the evidence for the absence of a meaningful effect, we performed equivalence tests for each meta-analysis, using the two one-sided test (TOST) approach (Lakens, 2017). We compared equivalence bounds using $r=\pm0.1$, $r=\pm0.2$ and $r=\pm0.3$ as the smallest effect sizes of interest, corresponding to conventional levels of small, medium and large effect sizes (Gignac & Szodorai, 2016). Effect sizes (Pearson's r coefficients) were converted to Cohen's d prior to equivalence testing (TOSTER (Lakens, 2017)). Summary effect sizes for all traits were statistically equivalent to zero when using equivalence bounds of $r=\pm0.3$, indicating evidence for an absence of any large effect (i.e. $r>0.3$ or $r<-0.3$) of personality on placebo effects. For equivalence bounds of $r=\pm0.2$, associations between placebo responsiveness and Behavioral Inhibition, Fun seeking, Goal-drive persistence, and Optimism were statistically equivalent to zero. For small effects (equivalence bounds $r=\pm0.1$), we did not find evidence for statistical equivalence. Thus, although there were no significant associations between placebo effects and any of the personality traits, we cannot rule out the possibility of a small effect ($r<0.2$) that may be detected with increased statistical power.
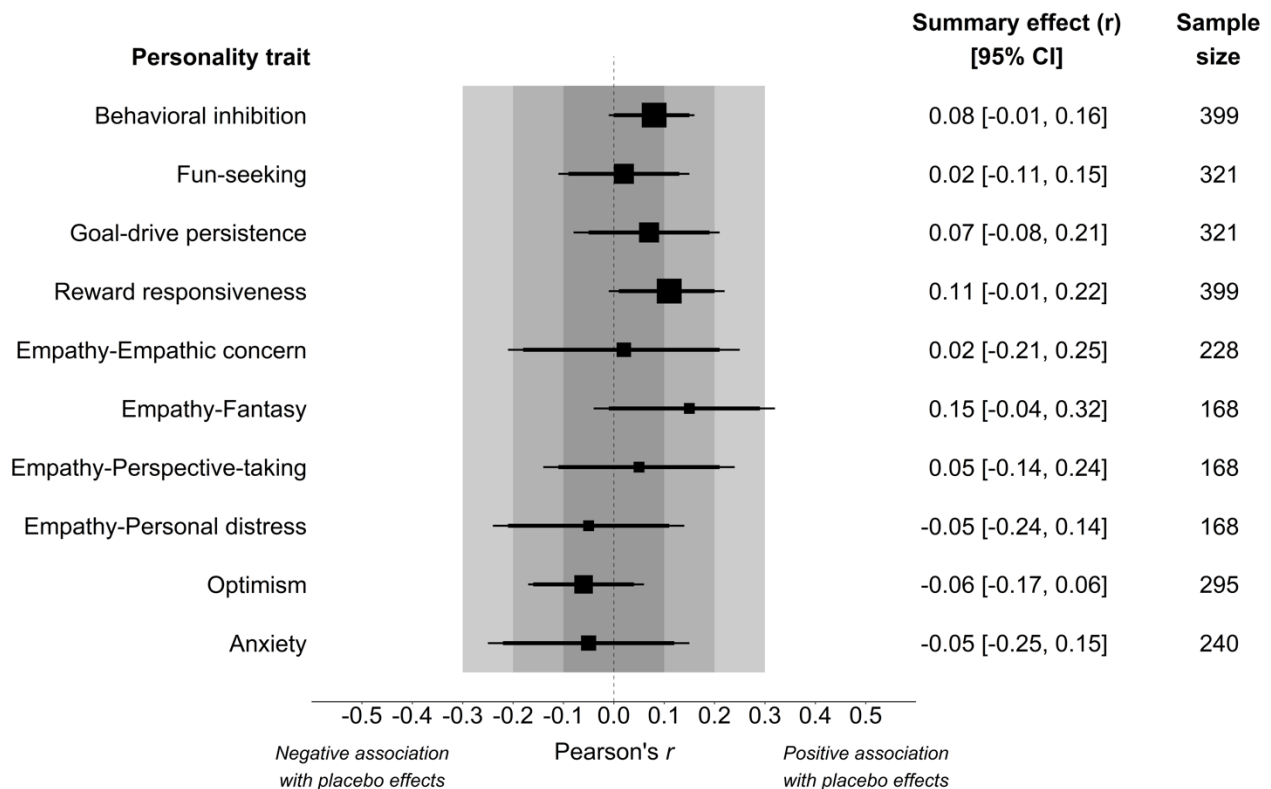

Personality trait		Summary effect (r) [95% CI]	Sample size
Behavioral inhibition		0.08 [-0.01, 0.16]	399
Fun-seeking		0.02 [-0.11, 0.15]	321
Goal-drive persistence		0.07 [-0.08, 0.21]	321
Reward responsiveness		0.11 [-0.01, 0.22]	399
Empathy-Empathic concern		0.02 [-0.21, 0.25]	228
Empathy-Fantasy		0.15 [-0.04, 0.32]	168
Empathy-Perspective-taking		0.05 [-0.14, 0.24]	168
Empathy-Personal distress		-0.05 [-0.24, 0.14]	168
Optimism		-0.06 [-0.17, 0.06]	295
Anxiety		-0.05 [-0.25, 0.15]	240

-0.5 -0.4 -0.3 -0.2 -0.1 0.0 0.1 0.2 0.3 0.4 0.5

Negative association with placebo effects Pearson's *r* *Positive association with placebo effects*

Figure 2. Summary of meta-analytic outcomes. The forest plot shows the summary effect of the placebo effect Vs. trait correlation for each personality trait. The size of each square (summary effect) corresponds to the total sample size, and the thin lines represent 95% confidence intervals (CI), relevant to the Robust Variance Estimation. A more positive summary effect reflects a positive association between a given personality trait and placebo effects – i.e. individuals with a high trait

score would benefit more from placebo treatment – whereas a negative summary effect reflects a negative association between trait and placebo effect. The thick lines represent the 90% CI, relevant to the two one-sided tests (TOST) for statistical equivalence. Specifically, a summary effect is equivalent to zero if the 90% CI does not extend past the upper or lower bounds (shaded in grey for bounds corresponding to r=±0.1, r=±0.2, and r=±0.3).

Influence of moderators

Moderate or high heterogeneity across studies (I^2>25%) was observed for the traits Fun seeking (I^2=27.70), Reward responsiveness (I^2=29.73%), Empathy – Empathic Concern (I^2=50.16%), and anxiety (I^2=29.64%). We performed the following subgroup analyses to investigate potential sources of this heterogeneity, using a similar statistical approach as for the main meta-analyses (k≥5 effect size estimates): placebo manipulation method (Conditioning, Non-conditioning) and condition studied (Pain, Non-pain).

The summary effect for each subgroup was calculated under random effects model incorporating RVE, similarly to the main analyses. However, the degrees of freedom for some subgroups fell below df=4, which limits the interpretability of the results: Fun seeking – non-pain (df=1.91), involving conditioning (df=1.98); Reward responsiveness – non-pain (df=1.98), involving conditioning (df=2.24); Empathic concern – involving conditioning (df=2.77). Therefore, the results of these subgroup analyses should be taken as preliminary. Subgroups were then compared using random-effects meta-analysis. Results did not indicate a significant difference for any of the subgroup analyses (**Table 2**).

Table 2. Results of subgroup analyses

Subgroup	N studies	N effect sizes	Summary effect			Heterogeneity		
			r	95% CI	P	r_{diff}	Z	P
Fun Seeking								
Condition studied						0.06	0.77	0.44
Pain	8	18	0.04	[-0.12, 0.20]	0.59			
Non-pain	3	5	-0.03	[-0.24, 0.19]	0.65			
Placebo manipulation method						0.20	0.94	0.35
Involving conditioning	3	10	0.18	[-0.63, 0.80]	0.49			
Not involving conditioning	6	13	-0.02	[-0.11, 0.07]	0.52			
Reward Responsiveness								
Condition studied						0.12	0.76	0.45
Pain	9	22	0.09	[-0.03, 0.21]	0.12			
Non-pain	3	5	-0.03	[-0.59, 0.55]	0.87			
Placebo manipulation method						0.02	0.23	0.82
Involving conditioning	4	10	0.11	[-0.05, 0.27]	0.10			
Not involving conditioning	6	17	0.09	[-0.14, 0.31]	0.36			
Empathy – Empathic Concern								
Placebo manipulation method						0.05	0.24	0.81
Involving conditioning	4	9	0.05	[-0.43, 0.51]	0.77			
Not involving conditioning	7	7	<0.01	[-0.36, 0.36]	0.99			

r=Pearson's r. rdiff=raw difference between subgroups, Z=standardized difference between subgroups.

Sensitivity analyses

In order to identify potential outlier effect sizes, we first performed influence tests for each meta-analysis, which identified one outlier for Reward Responsiveness (De Pascalis & Scacchia, 2019) and Empathy – Fantasy (Corsi & Colloca, 2017). No outliers were identified for any of the other traits. To assess sensitivity, we performed separate meta-analyses for 'Reward Responsiveness' and 'Empathy – Fantasy' with these effect sizes excluded. The results for both traits were statistically comparable with the original analyses (Reward Responsiveness: r=0.06 [-0.01, 0.13], P=0.07, I^2=8.17%; Empathy – Fantasy: r<0.01 [-0.13,0.14], P=0.94, I^2=0%) (De Pascalis & Scacchia, 2019).

Second, we conducted sensitivity analyses by re-running meta-analyses with unpublished data excluded. These analyses indicated slightly larger effect sizes for Behavioral inhibition (r=0.10 [0.03, 0.18], P=0.02, I^2=0%) and Reward responsiveness (r=0.17 [0.04, 0.30], P=0.02, I^2=17.20%), compared to the original analyses. This is consistent with the tendency that unpublished results are more supportive of the null hypothesis, compared to published studies (Polanin et al., 2016).

Impact of publication year and study quality

We performed meta-regression to investigate effect of study quality and publication year on the absolute effect estimates. Observed effect sizes (Pearson's r) of the individual reports were plotted against study quality (**Figure 3A**) and publication year of included studies (from 2009 to 2020) (**Figure 3B**). Results indicated no significant effects of study quality (B=0.01, P=0.58) or publication year (B=-0.01, P=0.29).

Figure 3. Meta-regression investigating the impact of study quality and publication year on outcomes, across all traits. Filled circles represent individual effect sizes, and circle sizes represent their corresponding weights in the regression model. The shaded area surrounding the regression line represents 95% confidence intervals. A) There was no significant association between study quality and effect size (Pearson's r) B=0.01 (P=0.58). B) There was no significant association between publication year and effect size (Pearson's r) (B=-0.01, P=0.29).

Risk of bias

We developed a customized assessment tool to evaluate study quality (see **Table S1**). Next, we rated overall risk of bias based on study quality score of each study such that low, moderate, and high study quality correspond to high, moderate, and low risk of bias, respectively. Overall, we found the main reason for downgrading was the use of a single-blind design without assessing the success of blinding.

We assessed risk of reporting bias in syntheses with all personality traits collapsed to investigate the literature as a whole. We did not identify publication bias from the contour-enhanced funnel plot (**Figure 4**). An Egger's sandwich regression test confirmed that the observed effects did not indicate risk of reporting biases in the synthesized literature (B (se)=0.71 (0.61), P=0.14). In addition, we performed a sensitivity analysis using robust estimation to accommodate clustering, to estimate how much more likely affirmative studies are published compared to non-affirmative studies (Mathur & VanderWeele, 2020). We defined studies as affirmative when the effect estimate was positive and statistically significant (α<0.05). We combined effect size estimates from all personality traits to assess the literature as a whole. For traits hypothesized to be negatively associated with placebo effects (i.e. Anxiety and Behavioral inhibition), the signs of effect estimates were therefore reversed prior to analysis. This analysis indicated that, for publication bias to shift the summary effect estimate to the null, affirmative studies would have to be 1.10 times more likely to be published than non-affirmative studies. This suggests that the primary meta-analytic results are robust to publication bias, which is in line with the results of the contour-enhanced funnel plot and the Egger's sandwich regression test.

Figure 4. Contour-enhanced funnel plot. Effect sizes are plotted against their standard errors for visual inspection of publication bias. Published data are represented as black points and unpublished data and represented by red points. The vertical line represents the overall effect size, and the shaded areas represent bounds corresponding to different p-value cut-offs, as indicated in the key. The plot does not suggest asymmetry or risk of publication bias, which would be indicated by over-representation of data points in the contour-shaded areas.

Discussion

Despite the common presumption that personality is a key factor for placebo responsiveness, our preregistered systematic review and meta-analyses did not find evidence that personality traits are associated with magnitude of placebo effects. This null finding applied to all traits assessed, and we did not find evidence that moderators such as condition (pain or non-pain) or placebo manipulation method (conditioning or non-conditioning) affected the association between personality and placebo effects. Moreover, equivalence tests supported the absence of any meaningful effects of medium-to-large magnitude for most traits, but we cannot exclude potentially small effects that may have been undetected due to insufficient power.

Overall, the results do not support the hypothesis that personality plays a meaningful role in shaping placebo effects. Thus, personality metrics, by themselves, do not appear promising as predictors of placebo responsiveness. More broadly, these results raise questions about whether there may be other dispositional factors that may influence placebo responding, or whether differences in placebo responsiveness are mostly due to situational and learning-based factors such as expectations (Corsi & Colloca, 2017; Peerdeman et al., 2016), social context and rapport with the clinician (Ferreira et al., 2013; Kaptchuk et al., 2020; Kelley et al., 2009), attentional processes (Geers et al., 2006; Rossettini et al., 2018; Sprenger et al., 2012), mood and affect (Elsenbruch et al., 2019; Geers et al., 2019; Morton et al., 2009) or associative conditioning (Jensen et al., 2012; Montgomery & Kirsch, 1997; Stewart-Williams & Podd, 2004).

Several non-personality dispositional factors have been investigated. Genetic factors have been proposed to play a role in influencing the placebo effect (Hall et al., 2015). In particular, genetic variation in neurotransmitter systems that have been linked to placebo effects, e.g. endogenous dopamine (De la Fuente-Fernández et al., 2001; Scott et al., 2008), opioid (Pecina et al., 2015), serotonin (Furmark et al., 2008), and endocannabinoid functioning(Benedetti et al., 2011) have been highlighted as promising. Furthermore, relatively stable brain parameters such as cortical thickness (Vachon-Presseau et al., 2018), grey matter volume (Vachon-Presseau et al., 2018) and density (Schweinhardt et al., 2009) of cortical regions and subcortical nuclei, white-matter connectivity (Stein et al., 2012), and functional (resting state) network connectivity (Tétreault et al., 2016) have been linked with individual magnitude of placebo analgesia. While these findings are promising, the heterogeneity in methodology between these studies makes it challenging to identify factors that may generalize across different contexts. However, a recent meta-analytic effort synthesizing task-related fMRI from individual participants discovered a pattern of task-related circuitry associated with individual differences in placebo effects across heterogeneous studies (Zunhammer et al., 2021). Linking placebo outcomes with stable MRI parameters from this consortium dataset (structural MRI parameters and resting state network connectivity) may reveal potentially generalized dispositional brain parameters.

One interesting characteristic of the identified literature is that, while influential studies formulated hypotheses about "placebo reactor personality" as early as 1954 (Lasagna et al., 1954), the eligible studies were notably recent, with the earliest eligible study published in 2009. Importantly, we did not use any restrictions based on publication year. The primary reason for ineligibility for pre-2009 studies in this review was the lack of within-subjects assessment of placebo effects and the lack of a no-treatment control group. Another observation is that the majority of the included studies investigated placebo effects for pain - we identified 141 effect sizes that were pain-related and 30 non-pain outcomes (e.g. stress, tactile pleasantness, exercise performance). This is reflective of the experimental placebo literature as a whole, in which pain is most extensively studied, whereas less is known about placebo effects in other domains (Weimer et al., 2020).

The included studies had risk of bias ranging from low to high. We identified suboptimal experimental blinding as a key risk factor. Specifically, the majority of studies adopted single-blinded designs, in which participants were blinded to the condition (placebo/control) but the experimenter was not. This is concerning, given previous reports of that experimenters' expectations can affect patient outcomes (Chen et al., 2019; Gracely et al., 1985). In addition, most studies did not state whether blinding success was assessed. This is also a broader issue in randomized-controlled trials, in which unsuccessful blinding is a known source of bias (Fergusson et al., 2004).

For some personality traits, such as optimism, the outcomes of our syntheses may seem at odds with some previous systematic reviews (Horing et al., 2014; Jakšić et al., 2013; Kern et al., 2020). For example, a recent systematic review concluded that optimism may be a positive predictor of placebo responses, since a majority of the identified studies were consistent with a hypothesis that higher

optimism/lower pessimism is associated with improved placebo response or reduced nocebo response (Kern et al., 2020). There are several differences in the selection process and general scope between our review and previous endeavors (Horing et al., 2014; Jakšić et al., 2013; Kern et al., 2020) that are worth discussing, and which may have contributed to these apparent discrepancies in outcomes.

First, we only included studies that used a no-treatment control for the placebo condition (i.e. "placebo effect"), which led to the exclusion of several studies (e.g. most clinical trials) that investigated "placebo responses" as operationalized in clinical trials, e.g. a change in symptoms after placebo treatment relative to a pre-placebo baseline (Horing et al., 2014; Jakšić et al., 2013; Kern et al., 2020). We applied this relatively strict eligibility criterion because we sought to minimize the influence of factors such as natural history, spontaneous remission, and regression to the mean (Fisher, 1967; McNair et al., 1979). For example, a positive association between a given trait and placebo response (change in pain after, relative to before, placebo treatment) could be driven by a tendency for such people to "naturally" recover more quickly, or show a higher frequency of fluctuations in symptomology, during a trial. Alternatively, such an effect could reflect a stronger tendency to sign up for a trial or research study when symptoms are particularly bad, relative to their usual state, increasing the risk of regression to the mean as a bias. The inclusion of a no-treatment condition controls for these factors when compared to a placebo treatment condition, and thus represents a less biased indicator of outcome change due to psychosocial processes (Kienle & Kiene, 1997; Kirsch, 2013).

Second, we included unpublished studies in our study. While the inclusion of unpublished studies increases statistical power, such studies often show weaker statistical effects compared to published studies. Indeed, sensitivity analyses indicated that, for Behavioral inhibition and Reward responsiveness, there was a modest tendency toward lower effect sizes for unpublished relative to published studies. A common explanation is the file drawer effect, i.e. that researchers and journals are less inclined to publish null or negative findings compared to positive findings (Rosenthal, 1979). Thus, the inclusion of unpublished studies is thought to improve the accuracy of meta-analytic estimates, and is generally a recommended practice. There may of course other reasons for why studies are unpublished, including low study quality, methodological errors, or failed manipulation checks. However, this did not seem to characterize the current dataset. In fact, a direct comparison showed that unpublished studies were scored higher on study quality compared to published studies (published vs. unpublished: t(83.31)=-9.36, P<0.001). Another possibility is that the unpublished relative to the published subsample may consist of more reports in which personality was a secondary or exploratory outcome. However, even for published reports, it is difficult to accurately assess post hoc whether an outcome was indeed a primary or secondary outcome originally, especially in non-preregistered studies and in studies not including an a priori power analysis. Thus, we did not attempt to assess the impact of whether-or-not outcomes were primary or secondary.

Third, we focused on placebo effects in our meta-analyses, and did not consider studies investigating personality and nocebo effects (i.e. symptom worsening in response to placebo treatment). Although there may be overlapping processes involved, methodological approaches to induce placebo and nocebo effects are often very different, making them challenging to combine directly in a meta-analysis. Thus, we chose to limit the scope to placebo effects in this study. Consequently, several studies investigating associations between optimism/pessimism and nocebo effects were omitted(Corsi et al., 2016; Geers et al., 2005; Szemerszky et al., 2010).

Finally, since our meta-analyses synthesized correlation coefficients, we excluded studies using stratification or post-hoc subgrouping based on personality trait scores, e.g. comparing placebo effects between "high score" relative to "low score" groups (Geers et al., 2005). The heterogeneity of experimental designs and analysis approaches for stratification studies make them challenging to subject to formal meta-analysis, especially in combination with reports of correlation coefficients. Our approach has the advantage of utilizing non-reductionist individual gradations of both trait scores and placebo outcomes. Yet, it is possible that certain personality traits may have indirect non-linear, conditional, or moderating effects on placebo responding, in combination with situational factors, that were not captured by our linear approach. For example, it has been proposed that placebo responding may depend on the degree to which environmental cues in the therapeutic context are congruent with individuals' "avoidance" and "approach"-related personality traits (Darragh et al., 2015). One study found a positive association between placebo improvement and trait extraversion, agreeableness and openness (approach-related traits), but only in the context of a warm

therapist-patient interaction (Kelley et al., 2009). Another study found that participants with higher empathic concern showed stronger placebo analgesia when expectations were transmitted via social observation of others, but not in a "verbal suggestion alone" condition (Hunter et al., 2014).

We identified small-to-moderate heterogeneity between study effect sizes in our meta-analyses. To investigate the heterogeneity of effect estimates between studies, we sought moderators for empathic concern, fun-seeking behavior, and reward responsiveness, which met our criteria for subgroup analysis eligibility. Notably, prespecified subgroups did not differ significantly by studied condition (i.e. pain vs non-pain studies) and placebo manipulation method (i.e. involving vs not involving conditioning). While these findings do not provide supporting evidence for contextual moderators such as type of placebo paradigm, material, and manipulation method, these subgroup analyses are limited due to sample size. Thus, more research is needed to determine how personality may potentially interact with situational factors, such as situational expectancy and the patient-clinician interaction (Ellingsen et al., 2020), to shape placebo effects. One approach could be to launch a "many-labs" project similar to efforts in psychology (Klein et al., 2014, 2018), in order to yield enough statistical power to detect such nuanced effects.

In addition to these limitations, the number of included studies and their sample sizes were relatively limited and thereby meta-analyses may be underpowered to detect a small but meaningful effect. It should be also noted that we could not perform meta-analysis on other personality traits that have been linked to placebo effects (e.g. extraversion, neuroticism, pain catastrophizing) because the statistical power was insufficient to satisfy the assumptions of Robust Variance Estimation.

In conclusion, our systematic review and meta-analyses do not support an association between personality traits and placebo effects. This may suggest that individual variability in placebo responding may be better explained by situational and learning factors, or dispositional factors other than personality (e.g. genetic or stable brain phenotypes). However, due to a limited number of studies eligible for follow-up analyses into moderators such as condition (e.g. pain, non-pain), placebo manipulation method, and type of placebo, there may be potential interactions between personality and context factors that are eluded by the present approach. Given the substantial heterogeneity in study design in the current literature, a more structured large-scale approach may be necessary to investigate such potential personality-context interactions in placebo effects.

Methods
Eligibility criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews (Page et al., 2021). We surveyed the literature and included studies as eligible if they met all the following criteria: (1) inclusion of a no-treatment control condition (most randomized controlled trials, which usually lack a no-treatment control condition, were ineligible); (2) 'placebo effect' which was operationalized as the within-subject difference between a 'placebo' and a 'no-placebo/control' condition (i.e. studies in which the placebo effect is quantified as a between-group difference were ineligible); (3) individual assessment of personality/psychological traits (i.e. stratification studies comparing subgroups scoring "high" vs. "low" on a given trait were ineligible). In order to maximize statistical power and to account for publication bias, e.g. the file drawer effect (Rosenthal, 1979), we considered both published and unpublished data as eligible. Only publications in English language were included, and we applied no restrictions regarding publication year.

Literature search

Information sources and search strategy. Literature search was performed in two stages. In stage 1, from 4 to 16 December 2020, primary studies and review articles were systematically searched on Web of Science, PubMed, Embase, Google Scholar, and the Journal of Interdisciplinary Placebo Studies (JIPS) database (https://jips.online/), in line with previous recommendations (Bramer et al., 2017). For Google Scholar, we used the first 200 results sorted by relevance. In stage 2, on 8 January 2021, we searched relevant reference lists within published research papers and review papers that were already identified from the first search, in order to identify potentially eligible studies that were neglected during stage 1. Finally, we contacted authors from studies that did not report collecting

personality trait data, but which otherwise met the eligibility criteria, to request any eligible un-published data.

Search terms were specified to retrieve studies that operationalize placebo effect and personality traits and report correlation as outcome (Table S2). From the preliminary literature search, we experienced that placebo response and placebo effect were interchangeably used to refer the operationalization of placebo effect in this thesis. Search keywords included therefore both 'placebo response' and 'placebo effect'.

Study selection and data collection. Results of the systematic literature search were recorded using End-note version 9.3.3 (Clarivate, Philadelphia, US). After removing duplicates following the strategy suggested by Bramer et al. (Bramer et al., 2016), authors HK and MM independently screened titles, abstracts, and full-texts for inclusion. Ineligible studies were excluded in a stepwise process using the following order: (1) lack of no-treatment control condition; (2) 'placebo effect' not operationalized as within-subject difference between placebo and control condition (e.g. separate 'placebo' and 'control groups'); (3) no individual assessment of personality/psychological traits (e.g. only comparison between subgroups of participants with 'high' vs. 'low' trait scores). In the case of disagreement between the reviewers in this process, this was consulted with author DME and resolved through consensus.

Next, we extracted characteristics of studies: authors, publication year, sample size, demographics of participants (clinical vs non-clinical population, mean age, sex). Correlation coefficient (Pearson's r or Spearman's rho) of personality trait score and magnitude of placebo effect was extracted as the primary outcome. Experimental methods were also recorded: type of personality trait questionnaire, placebo manipulation method (conditioning, non-conditioning), target of placebo intervention (pain, anxiety, depression etc.), type of placebo treatment (drug, device, visual stimuli), and blinding (deceptive single-blinded, deceptive double-blinded, open-label).

We recorded 'placebo effect' outcomes if they reflected subjective or behavioral outcomes indicative of symptom improvement or other beneficial effect, ascribed to the administration of placebo (e.g., reduction in pain, improved anxiety/mood, increased positive affect, improved physical performance). Thus, we excluded any placebo-related change in biological/physiological metrics (e.g., brain activity or autonomic outflow), since these are not directly reflective of symptom improvement or other beneficial/desirable outcome. Any ambiguity was consulted with author DME for final decision.

In cases when potentially eligible correlational data were not reported in the published report, we contacted the corresponding author to request either the respective correlation coefficient or subject-level data on placebo effects and trait scores.

Risk of bias assessment

Most of the available tools for risk of bias assessment in meta-analyses are designed for clinical trials (e.g. Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins et al., 2011)), and not well fitted to experimental studies such as the literature reviewed here. Thus, we designed a custom study risk of bias assessment tool, based on a previous validated tool, the Oxford Quality Scoring system, which entails randomization, blinding and justification for data exclusion (Jadad et al., 1996) (for details, see **Table S1**).

Using this custom risk of bias tool, study risk of bias was independently assessed by two review authors (HK and MM). Any disagreement was solved through discussion and consulted with the author DM when consensus could not be reached. Total risk of bias was computed as sum of six criteria, which we broadly categorized into low (0-2), moderate (3-4), high (5-6) quality. These scores were interpreted as implicating high, moderate, and low risk of bias, respectively.

Effect measures

The effect size measure of interest was the correlation coefficient between the placebo effect and personality trait score. Since studies define the 'placebo effect' differently (e.g. placebo – control vs. control – placebo), we inversed the sign for relevant studies such that a positive correlation

coefficient indicated that a higher trait score was associated with better outcome improvement (e.g., larger reduction in pain) in the placebo condition relative to control.

Data synthesis

Eligibility for each synthesis. Since studies have typically reported independent theoretical rationale for testing the association between placebo effect and a given trait, we performed separate primary meta-analyses for each identified trait. We pursued formal meta-analyses of traits when the final eligible sample included at least five effect sizes, in line with previous recommendations (Fu et al., 2008; Tipton, 2015), and satisfied the statistical assumptions of Robust Variance Estimation (See 'Multiple outcomes within a study' section). Using these criterion, primary meta-analyses were performed for following personality traits with a priori significance level, $\alpha=0.05$: Behavioral inhibition, Fun seeking, Goal-drive persistence, Reward responsiveness, Empathic concern, Fantasy, Perspective-taking, Personal distress, Optimism, and Anxiety.

Data preparation. We extracted Pearson's r coefficients as the primary outcome. In cases where unpublished individual subject data was obtained, we calculated Pearson's r coefficients based on those raw data. For studies that reported Spearman's rho, we converted these coefficients to Pearson's r (Rupinski & Dunlap, 1996). All coefficients were then converted to Fisher's z for computing summary effects and confidence intervals, and were converted back to Pearson's r for reporting purposes, as recommended by Borenstein et al. (2011). Effect sizes r=0.10, r=0.20, r=0.30 were interpreted as arbitrary levels for small, moderate and large effects, respectively, following Gignac and Szodorai's recommendation for individual difference studies (Gignac & Szodorai, 2016).

Presentation of data synthesis. Characteristics of the identified studies were summarized in a table ordered by publication year (**Table S3**). Results of individual studies and data synthesis for each personality trait were presented in individual forest plots (**Figures S1-S10**). In each forest plot, individual studies were visualized by squares, indicating point estimates and 95% confidence intervals, and the size of squares representing the weight assigned to them. The summary effect size and its 95% confidence interval were displayed as polygon at the bottom of forest plot. The effects of all meta-analyses were summarized in a summary forest plot (**Figure 2**).

Model for data synthesis. All analyses were performed in RStudio (version 4.0.4). We used robumeta (version 2.0) (Fisher et al., 2017) for random-effects model meta-analysis with the Robust Variance Estimation; metafor (version 2.4-0) (Viechtbauer, 2015) for data visualization; pimeta (ver 1.1.3) (Nagashima et al., 2019) for prediction intervals; TOSTER (ver 0.3.4) (Lakens, 2017) for equivalence testing; PublicationBias (ver 2.2.0) (Mathur & VanderWeele, 2020) for sensitivity analysis of publication bias.

Due to the use of different modes of placebo manipulation and outcome measures in each study, it was unlikely that populations in all studies included in this meta-analysis shared one single true effect. Therefore, the summary effect size and confidence interval were estimated using a random-effects model. Under a random-effects model, it is assumed that observed difference between individual studies consists of sampling error and heterogeneity in true effect size. The between-studies heterogeneity was quantified and tested using I^2-statistic, with the null hypothesis that there is no heterogeneity between studies. We conducted a relevant subgroup analyses when moderate heterogeneity was observed, $I^2>25\%$, following the Cochrane Handbook (Deeks et al., 2011).

We also computed prediction intervals to estimate the extent to which a true effect estimate from a future study might fall into based on the identified studies (Borenstein et al., 2011; Higgins et al., 2009). It represents the actual dispersion of effect sizes around the summary effect, providing an explanation for heterogeneity in addition to I^2-statistic. In this review, 95% prediction intervals were presented along with summary effect estimate and confidence intervals for each individual trait.

Multiple outcomes within a study. Studies commonly report multiple outcome measures from the same dataset (e.g., the correlation between a given trait and separate placebo outcomes), which can lead to statistical dependency. We expected the main source of shared variance to be introduced by shared samples (e.g., different outcomes derived from the same sample and data collection), whereas we expected less dependence between effect sizes obtained from different groups, even when they were part of the same general data collection. Thus, multiple effect sizes from different experimental groups within a reported study were treated as independent. Multiple effect sizes from a study could also be observed when a study used two or more types of outcomes to measure placebo effect (e.g., pain intensity and pain unpleasantness), raising risk of shared variance.

We therefore conducted meta-analyses incorporating Robust Variance Estimation (RVE), a random-effects meta-regression developed to flexibly handle dependent effect size measures (Hedges et al., 2010). RVE can incorporate multiple dependent effect sizes within a study even without the knowledge of the correlation between effect sizes with adequate reliability, even with smaller samples (Tipton, 2015). We specified an intercept-only model to compute summary effect sizes. With the small sample adjustment, the degrees of freedom should be larger than 4 for reliable interpretation of the results. We used this parameter (df<4) as a decision criterion for whether-or-not to perform formal meta-analysis for a given trait (primary analyses).

Consideration of multiple comparisons. In meta-analytic investigations, it is common to perform multiple statistical comparisons, which may increase the risk of Type I errors. This is especially pertinent in the case of multiple equivalent or dependent comparisons assessing the same hypothesis, or in the case of exploratory analyses involving a large number of tests. There are several ways to account for this, though there is no consensus on which method is the most efficient. It is often suggested to use family-wise correction (Polanin & Pigott, 2015) or use a lower alpha level than the commonly used P=0.05, (i.e., P=0.01 or P=0.005) (Borenstein et al., 2011). However, an overly conservative correction can increase the risk of Type II errors (i.e. false negative results). In this investigation, we considered the main analyses (for each identified personality trait) as assessing relatively independent hypotheses for the association between personality and placebo effects, and thus did not apply correction for multiple comparisons with regard to the number of primary analyses.

Equivalence testing. We incorporated two one-sided tests procedure to statistically determine absence of a meaningful effect (Lakens, 2017). Levels for the smallest effect size of interest were set as r=0.10, r=0.20, r=0.30, based on Gignac & Szodorai's recommendation for effect sizes in individual difference studies (Gignac & Szodorai, 2016). Since TOSTmeta only supports Cohen's d effect size estimates, coefficients were converted to Cohen's d prior to equivalence tests.

Subgroup analyses. We performed subgroup analyses to investigate between-study variability. Subgroup factors were prespecified based on the previous studies that proposed that distinct mechanisms may be involved in different study conditions and characteristics (e.g. study condition (Pollo et al., 2011), type of placebo (Benedetti & Dogue, 2015), and placebo manipulation method (Colloca & Benedetti, 2009; Meissner & Linde, 2018)). However, due to the limited sample size, we were not able to use the full specter of levels specified in the preregistration (e.g. social observation, verbal suggestion, conditioning, semantic priming for the factor "placebo manipulation method"). As a consequence, we reduced the granulation of levels, and used the following factors and levels: Condition (pain, non-pain), Placebo manipulation method (conditioning, non-conditioning), and Type of placebo (drug, device). For example, the condition "non-pain" comprised studies of stress, fear, and physical performance; "drug" included topical cream, pill, or nasal spray as placebos; "device" included sham acupuncture, sham TENS, and sham neurostimulation; and "non-conditioning" included studies that used verbal suggestion and social observation to induce placebo effects. After studies within each personality trait category were divided by a priori subgroup levels, a summary effect size for each level was calculated. These subgroup-level effect sizes were then used to quantify the magnitude of heterogeneity between subgroups. Heterogeneity was investigated using a random-effects model.

Additionally, we performed a separate meta-regression with study quality and publication year, to investigate whether study quality and year of publication affected reported effect sizes. These analyses were performed with all personality traits collapsed as we were interested at the impact of two potential moderators in the placebo effect literature as a whole. Since the hypothesized

direction of the association differed between different traits, we used absolute values of effect estimates to conduct these analyses.

Sensitivity analyses. Sensitivity analyses were performed to evaluate whether the original results were robust to the decisions and assumptions made for the data synthesis. First, we used a leave-one-out method to assess the impact of outliers in the case that any outlier was identified from influence test (metafor package (Viechtbauer, 2015)). Second, for meta-analyses including unpublished data, we investigated whether summary effect sizes without unpublished data were substantially different from the original analyses.

Reporting bias assessment. Reporting bias can arise when studies tend to be disseminated based on direction of effect and its statistical significance. This may bias the reliability of summary effect size by increasing risk of under- or overestimate it. To examine reporting bias, we first generated a contour-enhanced funnel plot with all the traits collapsed (Peters et al., 2008; Sterne et al., 2011). However, funnel plot asymmetry does not necessarily indicate publication bias, and may reflect other sources of biases, between-study heterogeneity or randomness (Egger et al., 1997). Hence, we performed the Egger-sandwich regression test to investigate funnel plot asymmetry (Rodgers & Pustejovsky, 2020). Next, we tested sensitivity to publication bias using a Robust Estimation approach, which can accommodate clustered effect sizes, in order to assess the severity of publication bias (Mathur & VanderWeele, 2020). This analysis provides the likelihood of publication of affirmative study (i.e. a study effect favoring hypothesis and significant (P<0.05)) that could attenuate the summary effect to the null (r=0). By comparing results from primary meta-analysis to a worst-case meta-analysis in which only non-affirmative studies are included, this approach quantifies the severity of publication bias. This approach assumes one-tailed selection either favoring positive or negative result, which we determined based on the general hypotheses for each trait in the assessed literature. Specifically, the assessed literature generally hypothesized the traits Fun seeking, Goal-drive persistence, Reward responsiveness (Schweinhardt et al., 2009), Empathic concern, Fantasy, Perspective-taking, Personal distress (Colloca & Benedetti, 2009; Hunter et al., 2014; Valentini et al., 2014) and Optimism (Geers et al., 2005, 2007, 2010) to be positive predictors of placebo effects. We identified the traits Behavioral inhibition (Broelz et al., 2019) and Anxiety (Pecina et al., 2013) to be hypothesized to be negative predictors of placebo effects. Since we were interested in a general trend in the placebo personality literature, we inverted the sign of effect sizes for Behavioral inhibition and Anxiety, and performed the sensitivity analysis across all traits, under the assumption that publication bias favored positive and significant results over negative and non-significant results.

Registration and protocol. A preregistration of this meta-analysis protocol is publicly available in the PROSPERO database: (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020222637). PROSPERO is an international prospective register of systematic reviews of health-related outcome. The protocol was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Protocol (PRISMA-P) (Moher et al., 2015). The contents of the protocol include the rationale, research question, inclusion criteria, and plan for the meta-analyses and additional analyses.

We made a change to eligibility criteria for running subgroup analysis. In the preregistration, we stated that subgroup analysis will be conducted when the number of effect sizes per subgroup >10. Instead, we performed subgroup analysis when (1) moderate or higher heterogeneity was observed, i.e., $I^2 > 25\%$, and (2) when eligibility to run a random-effects model meta-analysis, i.e., the number of studies in a subgroup were 5 or higher. This change in protocol was decided after the initial search and eligibility assessment, and before any statistical analysis was performed.

Declaration of Conflicting Interests

Funding

Supplemental Material

Individual effect size data (correlation coefficients) and corresponding meta-data for all eligible studies are publicly available on Open Science Framework (https://osf.io/u9j2k/). Supplemental material for this article is available online.

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