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The influence of personality traits on the placebo/nocebo response

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Abstract: Objective: Some people might be more prone to placebo and nocebo responses than others depending on their personality traits. We aimed to provide a systematic review on the influence of personality traits on placebo and nocebo responses in controlled and uncontrolled studies. Methods: We conducted a systematic literature search in the databases CINAHL, AMED, PsycINFO and EMBASE for relevant publications published between January 1997 and March 2018. For all included papers, we conducted an additional forward search. Results: After screening 407 references, we identified 24 studies. The Big Five (i.e., neuroticism, extraversion, openness to experience, agreeableness and conscientiousness) and optimism were the most frequently investigated personality traits. Several studies found a positive association between optimism and the placebo response. Furthermore, we found that higher anxiety was associated with increased nocebo responses. Conclusion: Evidence points to a possible association between optimism and the placebo response. Therefore, further emphasising the investigation of the influence of optimism on the placebo/nocebo response seems warranted. For clinical practice, the impact of anxiety on the nocebo response might be important to identify patients who might be more prone to experiencing side effects of medical treatments.

DOI: <https://doi.org/10.1016/j.jpsychores.2019.109866>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-183343>

Journal Article

Accepted Version

Originally published at:

Kern, Alexandra; Kramm, Christoph; Witt, Claudia M; Barth, Jürgen (2020). The influence of personality traits on the placebo/nocebo response. *Journal of Psychosomatic Research*, 128:109866.

DOI: <https://doi.org/10.1016/j.jpsychores.2019.109866>

The influence of personality traits on the placebo/nocebo response: A systematic review

Running title: The influence of personality traits on the placebo/nocebo response.

Submission to Journal of Psychosomatic Research

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Abstract

Objective: Some people might be more prone to placebo and nocebo responses than others depending on their personality traits. We aimed to provide a systematic review on the influence of personality traits on placebo and nocebo responses in controlled and uncontrolled studies.

Methods: We conducted a systematic literature search in the databases CINAHL, AMED, PsycINFO and EMBASE for relevant publications published between January 1997 and March 2018. For all included papers, we conducted an additional forward search.

Results: After screening 407 references, we identified 24 studies. The Big Five (i.e., neuroticism, extraversion, openness to experience, agreeableness and conscientiousness) and optimism were the most frequently investigated personality traits. Several studies found a positive association between optimism and the placebo response. Furthermore, we found that higher anxiety was associated with increased nocebo responses.

Conclusion: Evidence points to a possible association between optimism and the placebo response. Therefore, further emphasising the investigation of the influence of optimism on the placebo/nocebo response seems warranted. For clinical practice, the impact of anxiety on the nocebo response might be important to identify patients who might be more prone to experiencing side effects of medical treatments.

Keywords: nocebo response, personality, placebo response, systematic review

Highlights

- Results on the influence of personality traits on placebo responses are heterogeneous.
- More studies are available on the influence of personality traits on the placebo response than on the nocebo response.
- Optimism seems to be positively associated with placebo responses.
- Anxiety might lead to increased nocebo responses.

1. Introduction

Placebo effects can be regarded as a desirable reaction to an otherwise inert intervention (such as an analgesic effect or an enhancement of performance) [1], whereas the nocebo effect represents its counterpart. A nocebo describes the noxious effect of the placebo [2] meaning the placebo intervention produces adverse side effects [3]. Additionally, a nocebo effect can also be regarded as a change in symptoms (such as an increase in pain) following a nocebo instruction [4]. Placebo and nocebo effects have been subjects of research for decades, as they might impact clinical outcomes [5]. These effects can be considered significant in pain and nausea and other patient-reported outcomes [6]. For antidepressant trials, it has been reported that the placebo effect accounts for up to 68% of the effect of the medication [7]. Based on those findings, it is advised to minimise placebo responses in clinical trials with placebo control conditions (to better detect the therapeutic benefit of the active intervention) whilst using their full potential in clinical practice [8]. Moreover, the nocebo phenomenon is linked to non-compliance and discontinuation of pharmaceutical interventions [9]. Placebo responses may depend on clinical conditions, type of outcome or patient-clinician interaction, but other factors at an individual level can also be meaningful. Genetics/biomarkers [10-12], learning and conditioning [6, 13, 14], individual expectations of a treatment outcome [15, 16] as well as personality [17, 18] are regarded as individual influencing factors on the placebo/nocebo response. In terms of personality, the question arises whether some people are more prone to placebo and nocebo responses than others. Consequently, it would be of interest to identify the

personality traits of a so-called placebo responder. By describing various shortcomings of previous placebo research (i.e., in terms of reliability and consistency of placebo responses), Kaptchuk and colleagues raised doubts about whether there is a *reliable* or *consistent* placebo responder [17]. Since other authors who investigated the influence of personality on the placebo/nocebo response have also seized upon these claims [19, 20] and several important studies on the topic have been published in recent years, it might be worth providing an update on the question of reliability and consistency of the association between personality and placebo/nocebo response. Authors like Darragh and colleagues [21] do not dismiss the idea of a placebo responder in general but suggest a rather transactional model, in which dispositional characteristics interact with environmental incidents.

In this review, we considered personality traits in a narrow sense, which is based on three decisions. First, we focused on prevalent and well-known personality traits (such as optimism or the Big Five). Second, we considered only studies with trait characteristics and ruled out studies on affective states. Third, we did not consider psychiatric conditions (such as depression or psychotic disorders) as traits since the placebo and nocebo effects in the psychiatric setting form another area of research with entirely different research questions [22, 23]. In summary, our systematic review includes studies about placebo and nocebo responses that investigated stable personality traits, which have been measured by self-report on established scales.

The decision to use the term *response* rather than *effect* is based on the following distinction. According to Enck and colleagues the placebo response (other than the effect) is based on the individual reaction to a placebo [24]. Furthermore, Benedetti

states that psychological mechanisms emphasise the multiplicity of placebo responses [25]. We therefore explored the concept of personality traits in the framework of responses rather than effects.

The aim of this systematic review was to provide an overview of the influence of personality traits on placebo and nocebo responses.

2. Methods

2.1. General eligibility criteria

We included studies with healthy subjects and patients of at least 18 years of age. Studies with patient samples were included independent of somatic diagnosis. We included randomised trials or cohort studies of subjects/patients receiving placebo or who were in a nocebo condition. Studies had to be published between January 1997 and March 2018 in English.

Our review includes placebo as well as nocebo studies. We split the inclusion criteria accordingly, since in terms of intervention, outcome and comparison group, the setup for placebo studies can differ from that for nocebo studies. Additionally, one single study can investigate both the placebo and nocebo response to an intervention.

2.2. Eligibility criteria for placebo studies

We included any type of placebo intervention. The comparison group had to include any type of placebo intervention or a control intervention. Studies had to report the extent to which personality traits were associated with the intervention (pre-post effect). The

outcome measures had to be clinically significant (in patients) or related to the intervention (in healthy subjects).

2.3. Eligibility criteria for nocebo studies

For the nocebo studies, we included any type of nocebo intervention in the intervention group. Pre-treatment briefings and information before a medical treatment were considered as interventions if they verbally put a strong emphasis on possible side effects of a treatment. For comparisons, the comparison group had to be a placebo or a no-treatment group, the study had to compare two placebo interventions, or the study had to compare two types of the abovementioned briefings/information. The study had to report the extent to which personality traits were associated with side-effect reporting or complaints, which was not necessarily the primary outcome of the study.

2.4. Search strategy and study selection

In a first step, we identified primary studies from reviews related to the topic and consecutively performed a hand search. In a second step, we conducted a systematic literature search in the CINAHL, AMED, PsycINFO and EMBASE databases. The terms “placebo effect*” OR “nocebo effect*” OR “adverse effect*” OR “placebo response” OR “nocebo response” were used. The additional search terms (names of personality traits and assessment tools) were connected with “AND”. The full list of keywords is provided in the appendix. Finally, for all included papers, we conducted an additional forward search.

After a training based on the coding manual, all steps in the screening and selection of the full text papers were performed in duplicate by AK and JB. All deviations in the codings were discussed and resolved in one final coding.

2.5. Data extraction

AK and CK conducted the data extraction and were trained beforehand in using the extraction manual. All studies were extracted in duplicate (AK and CK). In the case of coder disagreement, consensus was reached by a third party (JB). The full-scale data extraction codebook will be provided on request.

We extracted basic information about the study (last name of the first author, publication year and country where the study was conducted) as well as a brief description of the study context. Moreover, information about the sample (total sample size, mean age, subject characteristic healthy vs. patients) and the study design (randomised trial vs. cohort study) was extracted. The type of intervention (placebo vs. nocebo) was identified. Information about the personality traits, the study outcome and the finding (i.e., the effect of personality on the placebo/nocebo response) were extracted. Information about the type of effect of personality on the outcome was categorised based on whether it was a main effect or an interaction effect of the personality trait and the response to the intervention (placebo vs. control treatment).

Since the number of investigated personality traits in the studies was high, we decided to cluster some personality traits into larger concepts. We prepared a priori clusters for the traits based on relevant literature [26, 27]. The traits were clustered as follows: Openness to experience, conscientiousness (including self-directedness and

persistence), extraversion (including novelty seeking and reward dependence), agreeableness (including cooperativeness), neuroticism (including harm avoidance), optimism/pessimism, spirituality (including dispositional gratitude), somatisation (including somatosensory amplification), inhibition/activation (behavioural activation and inhibition system), social desirability, absorption (including imaginative involvement and self-transcendence), worry (including pain-worry), fear/anxiety (including fear of pain, pain anxiety and anxiety sensitivity), suggestibility, and other (including pain catastrophising, sensation seeking and interpersonal reactivity). This approach reduced complexity and allowed a larger number of studies to be related to one personality trait. We kept the descriptions of the personality traits as concrete as possible to offer an understanding of our findings to a readership that might come from a field other than psychology.

The effects of personality on the placebo/nocebo responses were evaluated by a vote counting approach, in which the number of studies with positive effects was compared to the number of studies with negative effects [28]. Since there is no consistent outcome measure across the studies we opted for this particular approach to get a summary of findings.

3. Results

3.1. Study selection and study characteristics

As figure 1 shows, we identified 425 references through database searching and an additional 40 through other sources. After the removal of duplicates and the subsequent

screening of titles and abstracts of 407 references, we included 40 references for full text evaluation. In total, 24 studies met our inclusion criteria [29-52]. All of the studies examined healthy subjects except for three studies. Kelley and colleagues (2009), looked at patients suffering from irritable bowel syndrome (IBS), Put et al. (2004) looked at asthma patients and Sullivan et al. (2008) had a sample of neuropathic pain patients. The 24 studies included 14 randomised trials and 10 cohort studies. In terms of interventions, 12 studies used a placebo intervention ([29], [30], [31], [32], [33-36], [37], [38], [39], [40]), 5 used a nocebo intervention ([41], [42], [43], [44], [45]), and 7 studies used both ([46], [47], [48], [49], [50], [51], [52]). Moreover, 14 studies investigated the effect of personality on the placebo/nocebo response based on interaction, and 10 studies investigated the effect based on main effect. A brief description of all studies included in this review is provided in table 1.

3.2. The Big Five

The Big Five (openness to experience, conscientiousness, extraversion, agreeableness and neuroticism) have gained ample attention in past studies concerning the association between personality traits and the placebo/nocebo response. Neuroticism was the most often reported personality trait, appearing in 10 studies; it was followed by extraversion (eight studies), conscientiousness (seven studies), agreeableness (six studies) and openness to experience (five studies). These studies are not mutually exclusive, meaning that one study can investigate more than one trait at a time. The results for the Big Five are provided in table 2.

3.2.1. Openness to experience

While neither Aslaksen and Lyby [41] nor Yu et al. [39] found an effect of openness to experience on the nocebo and placebo response, respectively, Beedie and colleagues [29] found that openness to experience was higher in placebo responders. An additional study [36] found that openness to experience was positively associated with the placebo response, but this result held for only one subgroup. Corsi and Colloca [46] found no effect of openness to experience on the placebo response, nor did they show an effect of the personality trait alone on the nocebo response.

3.2.2. Conscientiousness

None of the studies of Aslaksen and Lyby [41], Beissner et al. [30], Kelly et al. [36] and Yu et al. [39] found an effect of the conscientiousness trait on the placebo or nocebo response. Another study [46] showed no effect of conscientiousness on either response. Nevertheless, one study [29] found that high levels of conscientiousness were negatively correlated with physical performance in the placebo condition, and Corsi and colleagues [42] found that persistence was negatively correlated with the nocebo response.

3.2.3. Extraversion

Three studies found no effect of extraversion on the placebo or nocebo response [37, 39, 41]. Corsi and Colloca [46] found no effect of the trait on either response. However, Beedie et al. [29] showed that extraversion scores were substantially higher in placebo

responders. Another study, by Beissner and colleagues [30], showed that novelty-seeking scores were lower in subjects who were susceptible to placebo-induced sensations. Moreover, Kelley et al. [36] found extraversion to be the only independent predictor of the placebo response. Darragh et al. [31] found a trend of association between lower extraversion and greater benefit from the placebo intervention.

3.2.4. Agreeableness

Three of the six studies that examined agreeableness found no effect of the trait on the placebo or nocebo response [30, 39, 41]. Corsi and Colloca [46] could not show an effect of agreeableness on either response. However, Beedie and colleagues [29] found that agreeableness was substantially higher in placebo responders. Another study by Kelley et al. [36], showed that agreeableness was positively associated with the placebo response but only for the augmented communication group.

3.2.5. Neuroticism

Studies by Beissner et al. [30], Kelley et al. [36] and Yu et al. [39] found no effect of the trait on the placebo response. An additional study [41] could not show an effect of neuroticism on the nocebo response. Studies conducted by Corsi et al. and Corsi and Colloca [42, 46] and by van Laarhoven et al. [50] found no effect of neuroticism on either the placebo or the nocebo response. In contrast, Beedie and colleagues [29] found that neuroticism was positively correlated with performance in placebo trials. This result is in line with an additional study [38] stating that neuroticism correlated positively with placebo analgesia. Furthermore, another study [31] found that higher neuroticism

was related to increased physiological placebo responses. Corsi et al. found in their 2016 study [42] that harm avoidance was positively correlated with the nocebo response.

3.3. Optimism/Pessimism

The optimism–pessimism spectrum was one of the most frequently examined personality trait clusters in the context of placebo and nocebo responses. Seven studies investigated optimism and pessimism with regard to the placebo response, and five studies analysed the effect on the nocebo response. While Corsi and Colloca [46] could not find any association between either personality trait and the placebo/nocebo response, Darragh et al. [31] found lower dispositional optimism to be correlated with increased perceived effects of the placebo substance. Geers and colleagues conducted three studies in total, exploring the effect of both optimism and pessimism on the placebo response. In their first study [47], they found no differences between optimists and pessimists in the conditional expectation group. Their second study [33] found dispositional optimism to be positively associated with better sleep quality in the placebo expectation condition, and their third study [34] found that dispositional optimism was associated with lower pain ratings in the placebo condition. Accordingly, Morton et al. [37] found dispositional optimism to be a significant predictor of the placebo response, whereas Hyland and colleagues [35] found no effects of the examined personality traits. Concerning the nocebo response, Corsi et al. [42] found a correlation between lower dispositional optimism and the tendency to perceive the negative effects of a treatment. A similar result was found by Geers and colleagues [47], who reported that pessimists

were more likely than optimists to follow the nocebo expectation in the deceptive-expectation group. Additionally, Szemerszky et al. [43] found an association between higher dispositional optimism and lower experienced symptom scores, whereas Webster et al. [44] were not able to find any effects of the investigated traits on the nocebo response. Taken together, four of the seven studies examined found positive effects of dispositional optimism on the placebo response (i.e., better sleep quality, less pain), and three of five studies reported negative effects for optimism on the nocebo response (i.e., experienced symptoms). In conclusion, optimism was relatively consistently associated with increased placebo responses (with the exception of Darragh et al.). Pessimism was relatively consistently associated with nocebo responses as well. Table 3 provides detailed results on the optimism-pessimism spectrum.

3.4. Worry/Fear/Anxiety

Overall, worry, fear and anxiety were among the less-examined personality traits in connection with placebo/nocebo responses. Five studies examined fear and anxiety, and one also examined worry in addition to fear and anxiety. Corsi and Colloca found no association between worry and either the placebo or the nocebo response [46]. However, in the same study, they found a negative association between fear of pain and the placebo response, as well as a positive correlation between anxiety sensitivity and the nocebo response. In a similar context, Aslaksen and Lyby found a positive association between fear of medical pain and nocebo hyperalgesia [41]. Corsi and colleagues stated in another study that anxiety was positively correlated with the

perception of the negative effects of a treatment [42]. An additional study found for the nocebo condition that high pain anxiety is associated with increased suffering as well as an increased placebo response [49]. The latter finding is in contrast to the aforementioned result by Corsi and Colloca, which found that there is a negative association between fear of pain and the placebo response. Nevelsteen found no association between anxiety and either the placebo or the nocebo response [51]. The results reveal that the role of fear and anxiety concerning the placebo response is contradictory and needs further clarification. Nonetheless, the results indicate that fear and anxiety are positively associated with the nocebo response and thus increase the probability for negative effects of a treatment. In table 4 we provide the detailed results on the worry, fear, and anxiety cluster.

3.5. Other Traits

As table 5 shows, the spectrum of other traits is a heterogeneous cluster that consists of a variety of personality traits such as spirituality, somatisation, inhibition/activation, social desirability, absorption, suggestibility, interpersonal reactivity, empathic concern, sensation-seeking and pain catastrophising. Hyland and colleagues [35] investigated the effect of spirituality on the placebo response, finding that spirituality correlated with and predicted the perceived change of symptoms after the placebo treatments. Beyond that, dispositional gratitude enhanced perceived sleep quality after the placebo treatment. Furthermore, Szemerszky and colleagues [43] as well as Witthöft and Rubin [45] examined somatisation and its effects on the nocebo response. They both found that somatisation and somatosensory amplification were positively correlated with

experienced symptoms. An effect of the behavioural activation system (BAS) on the placebo response was found by Darragh et al. [31], who reported that the subscales of fun and drive were negatively associated with the placebo response, while the reward subscale showed a positive association. In addition to the inhibition/activation dimension, Darragh and colleagues [31] investigated the effect of absorption and empathic concern on the placebo response as well. Higher absorption as well as lower empathic concern were associated with the effects of the placebo substance. Corsi and Colloca [46] examined the connection of suggestibility and pain catastrophising with the nocebo response. Both personality traits were positively correlated with the nocebo response. Sullivan et al. found that higher scores in pain catastrophising were associated with greater pain reduction in the placebo condition [40]. None of the studies found effects of social desirability on either the placebo or the nocebo response (e.g., [52]).

3.6. Data synthesis

Table 6 shows our findings on the effects of personality on the placebo/nocebo response as vote counting. Positive and negative studies were displayed and null findings were also reported.

4. Discussion

Our results showed that optimism/pessimism as well as fear and anxiety might affect the placebo and/or nocebo response. Optimism was relatively consistently associated

with increased placebo responses, whereas pessimism was relatively consistently associated with nocebo responses. Moreover, fear and anxiety seem to be associated with the nocebo response by increasing the tendency to perceive the negative effects of a treatment.

Our results do not deliver clear-cut evidence towards *the* stable placebo responder, since we were not able to identify a solitary personality trait that is exclusively related to placebo or nocebo responding. However, we underscore the importance of further exploration of optimism and anxiety in relation to the placebo/nocebo response.

Overall, more research with placebo interventions than nocebo interventions was published, which is expected because the placebo response has drawn more attention to date than the nocebo response, and the investigation of the placebo response has a longer history in research than the nocebo response (e.g., [53]). Our review showed a widely heterogeneous picture in terms of study context, placebo/nocebo interventions and, consequently, study findings. An illustrative example is the case of extraversion, for which evidence is contradictory and no pattern can be detected.

Our review adds to the already existing reviews about the prediction of placebo responses by personality traits. To our knowledge, it is the first extensive work that investigated the influence of personality traits on the nocebo response in addition to the placebo response. Since the interest in the nocebo response has risen over the last decade, we extended our research question accordingly. As suggested by Jaksic and colleagues [19] in their viewpoint article, we included studies beyond the pain context to investigate whether the results hold in other clinical conditions. Horing et al. conducted

a systematic review on the prediction of placebo responses and investigated personality traits among the predictors [20]. Their literature search was restricted to PubMed, which represented a major drawback of this work, and we thus extended our literature search to other databases.

In order to discuss our two main findings (the associations between optimism/placebo and anxiety/nocebo), we provide theoretically and empirically based mechanisms.

Carver and Scheier linked optimism to a number of positive health outcomes [54]. The authors argue that optimists and pessimists differ in terms of coping with stressful situations. Geers was among the first proponents of evidence for a moderating effect of optimism on the placebo response [33, 34]. In terms of mechanisms, Geers suggested that optimists are better at withstanding health challenges than pessimists because they focus on the placebo components of medical treatments. A further explanation could be that optimists influence the extent to which they persist in the treated state after a placebo intervention and interpret this state positively as a consequence [55]. Both explanations provided by Geers and Abhishek match Carver and Scheier's abovementioned narrative of improved coping mechanisms in optimists. However, Geers emphasises the importance of situational and contextual factors which collectively determine the placebo response [34].

Our review suggests an effect of anxiety on the nocebo response, which might be explained by neuroendocrine and biochemical mechanisms especially in nocebo hyperalgesia. This hyperalgesia might be based on the hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis [56] or the stronger activation of the

CCKergic System in subjects with high anxiety [56, 57]. From a cognitive perspective, Crichton and colleagues suggest the misinterpretation of symptoms of hypervigilance and anxiety as signs of illness as a possible mechanism of a stronger placebo response in anxious subjects [58]. The risk of misinterpretation increases if perceived symptoms are consistent with an individual's health concerns. It could be beneficial to understand what exactly causes this kind of hypervigilance in an individual. This could be media reports or special alertness caused by a patient-practitioner interaction, all the more important as some individuals might already have established health concerns from prior (negative) experiences.

4.1. Implications for research

The heterogeneity of findings demands further research attention. On a descriptive level, the diversity of study contexts and interventions may be responsible for diverse results. Another source of heterogeneity lies in the discrepancies of the assessments of the personality traits. An example of such discrepancy is the diversity of the assessments of the Big Five and the anxiety traits, where it is apparent that the very same construct is being assessed using different questionnaires. However, optimism seems to be an exception, since this trait was measured with the same questionnaire across all studies. This exception, in turn, might be an underlying reason for the unidirectional results. In sum, further investigation and replication studies for optimism and pessimism seem warranted since these characteristics provided the most promising results.

Placebo responders within a sample might obscure the effects of an additional treatment compared to placebo. A practicable approach for further research could be the identification of placebo-responsive participants in a pilot study, such as that performed by Beedie and colleagues [29].

On a more general note, neurobiological correlates to the placebo and nocebo responses might provide further answers to the question of how personality traits might influence these responses. Combining brain imaging techniques, information about personality traits and even genetic information (analogous to the studies by De Pascalis and Scacchia [32] and Yu et al. [39]) can help researchers understand placebo responses.

Another implication might be the addition of more factors to the equation. As Kelley et al. [36] and Webster and colleagues [44] suggest, it appears difficult to reduce the predictor of the placebo/nocebo response to one single factor. Especially in clinical practice, the isolation of a single factor seems unnatural. It is therefore warranted to take a more interactional approach, such as considering the personality of a patient in conjunction with context-specific factors (i.e., health care provider, current symptoms or prior experiences).

The route of placebo administration is a crucial addition to the list of context-specific factors, since open-label placebo (OLP) is currently a prominent subject of debate and new findings have been emerging over the last few years (e.g., [59-61]). To our knowledge, there is only one study to date that incorporated personality trait measures in an open-label placebo trial [62]. This study showed no effect of personality traits

(optimism/pessimism and openness to experience) on the placebo response. However, further studies on OLP and personality are needed in order to confirm this initial finding.

4.2. Implications for practice

The result indicating a positive association between fear/anxiety and the nocebo response is pertinent in the context of clinical practice. Following this finding, it seems to be beneficial for caregivers in the clinical setting to detect highly anxious individuals to minimise the experience of side effects in an intervention.

4.3. Limitations

There are three challenges to external validity that become apparent when more closely examining the characteristics of the included studies. First, the subjects included in the studies were often young. Second, more women were included in some studies, and one study exclusively included women. Third, apart from three exceptions, all of the included studies investigated only healthy subjects. Generalisability to patient populations is thus limited.

We chose a cut off of January 1997 in our search strategy. Our interest was to include the studies that make a valid contribution and to keep the review feasible; therefore, we decided to take a time frame of 20 years. However, we are aware of the potential limiting implications of this a priori restriction.

Given the small number of included studies per individual personality trait, we decided not to calculate a meta-analysis. Furthermore, we did not conduct a quality

assessment of the included studies, since the variation in the design of the studies does not allow a quality assessment across studies with one single measure.

We face a methodological challenge when comparing the studies included. 10 out of 24 studies reported main effects of personality traits on placebo/nocebo responses, rather than interaction effects of personality traits on placebo/nocebo responses compared to control conditions. We are well aware that results based on main effect do not deliver the same valid information as results based on interaction effects. However, we decided not to exclude the results based on main effects, because these studies also add information, especially when they contradict other findings. Since our review endeavours to be comprehensive we refrained from limiting ourselves to a certain design or context.

In order to facilitate the understanding of our results and to do the high amount of heterogeneity of personality traits justice, we opted for the solution of clustering our results. As an example, table 4 shows the anxiety cluster comprises measures of fear, anxiety and worry. Generally, we are well aware of the nuances between fear, anxiety and worry. However, the vast number of results led us to the choice of clustering.

Since our findings are based on post-hoc-analyses, we are confronted with the possibility of publication bias. It might be possible that some placebo/nocebo mechanism studies included measures of personality traits but never reported null findings. One possible solution could be a mandatory pre-registration for experimental studies to become accepted for publication.

Finally, we would like to address the limitation of trend interpretation. A major part of our studies showed a small sample size. Therefore, we cannot fully assume adequate power, which is the rationale for trend interpretation. Furthermore, in many of the studies we looked at a secondary analysis, though the power analysis was conducted for the primary analyses.

4.4. Conclusion

The interest in predictors of the placebo/nocebo response has increased over the past several decades, and more sophisticated research in this context based on more complex models has been conducted [21]. However, literature covering the topic of the influence of personality traits on the placebo/nocebo response is rather scarce and heterogeneous. Optimism and pessimism can be regarded as potential predictors of the placebo response that are particularly worth following up on. With special attention to clinical practice, the influence of fear and anxiety on the nocebo response represents another important direction for further investigations.

Acknowledgements / Funding

This study was funded by the Swiss National Science Foundation (Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung), grant No. 105319_159833.

Conflict of interest

The authors have no competing interests to report.

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Appendix. Search strategy for EBSCO (PsycINFO, CINAHL, AMED)

- S1. TI "adverse effect*" OR TI "placebo effect*" OR TI "nocebo effect*" OR TI "placebo response" OR TI "nocebo response" OR AB "adverse effect*" OR AB "placebo effect*" OR AB "nocebo effect*" OR AB "placebo response" OR AB "nocebo response"
- S2. TI somatization OR AB somatization
- S3. TI "health concerns" OR AB "health concerns"
- S4. TI "physical complaints" OR AB "physical complaints"
- S5. TI conscientiousness OR AB conscientiousness
- S6. TI extraversion OR AB extraversion
- S7. TI neuroticism OR AB neuroticism
- S8. TI "openness to experience" OR AB "openness to experience"
- S9. TI optimism OR AB optimism
- S10. TI pessimism OR AB pessimism
- S11. TI "social desirability" OR AB "social desirability"
- S12. TI fpi OR AB fpi
- S13. TI NEO-FFI OR AB NEO-FFI
- S14. TI mmpi OR AB mmpi
- S15. TI EPI OR AB EPI
- S16. TI 16pf OR AB 16pf
- S17. TI ias OR AB ias
- S18. TI LOT-R OR AB LOT-R

S19. TI 16 pf OR AB 16 pf

S20. TI LOT OR AB LOT

S21. TI "life orientation" OR AB "life orientation"

S22. TI "life orientation test" OR AB "life orientation test"

S23. TI "life orientation test revised" OR AB "life orientation test revised"

S24. TI "sixteen personality factor questionnaire" OR AB "sixteen personality factor questionnaire"

S25. TI "openness to change" OR AB "openness to change"

S26. TI hysteric OR AB hysteric

S27. TI hypochondriasis OR AB hypochondriasis

S28. TI "personality test" OR AB "personality test"

S29. TI "personality inventory" OR AB "personality inventory"

S30. TI "personality questionnaire" OR AB "personality questionnaire"

S31. TI "personality assessment" OR AB "personality assessment"

S32. TI somatisation OR AB somatization

S33. S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32

S34. S1 AND S33

LIMITERS

Date: 01.01.1997 – 31.03.2018

Source type: Academic journals, journals

English language; Exclude MEDLINE records; Human, Age Groups: All Adult

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	28-30 Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	-
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9
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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	22-23
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16, Tables 2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16 Table 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	22-23
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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