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Psychological factors related to time to help-seeking for cancer symptoms: A meta-analysis across cancer sites

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Abstract

The time patients wait before seeking help for cancer symptoms is among the most important factors contributing to diagnostic delays in cancer. We reviewed the association between time to help-seeking and three psychological factors: symptom knowledge, symptom interpretation, and beliefs about cancer (Prospero review protocol CRD42018088944). Forty-seven studies published between 1990 and 2019 met the inclusion criteria, providing data on 44,961 participants from 22 countries concerning seven cancer sites. A series of random-effects meta-analyses and meta-regressions were conducted. Better symptom knowledge was related to lower odds of a long help-seeking interval in both studies with healthy populations (OR=.73, 95% CI [.63, .84], k=19) and with patients (OR=.40, 95% CI [.23, .69], k=12), and so was interpreting experienced symptoms as cancer-related (OR=.52, 95% CI [.36, .75], k=13 studies with patients). More positive beliefs about cancer (i.e., that cancer is treatable) were associated with lower odds of a long help-seeking interval in both studies with healthy populations (OR=.70, 95% CI [.52, .92], k=11) and with patients (OR=.51, 95% CI [.32, .82], k=7). Symptom knowledge, interpretation, and beliefs about cancer are likely to be universal predictors of help-seeking. Theoretical models of patient help-seeking and interventions aiming to reduce delays should incorporate these factors.

Keywords: cancer; patient interval; time to help-seeking; diagnostic delay; beliefs; symptoms; knowledge

Psychological factors related to time to help-seeking for cancer symptoms: A meta-analysis across cancer sites

Delays in the diagnosis of cancer have been associated with less favourable patient outcomes across several types of cancer including breast, colorectal, head and neck, melanoma, and testicular cancer (Neal et al., 2015). Delays may occur at different stages of the diagnostic process generally referred to as the patient interval (the time from symptom onset to help-seeking, i.e., first consultation) and the diagnostic interval (the time from first consultation to diagnosis) (Walter, Webster, Scott, & Emery, 2012). Research shows that patient intervals could be two-to-five-fold longer than diagnostic intervals across multiple types of cancer (Allgar & Neal, 2005; Lyratzopoulos et al., 2015). This suggests that there is great potential to achieve earlier diagnosis and better outcomes for symptomatic cancers by reducing the patient interval. This can be achieved by individual interventions or large-scale information campaigns that address drivers of delayed help-seeking (Austoker et al., 2009; Power & Wardle, 2015). However, up to date there is limited evidence that such campaigns can successfully shorten help-seeking intervals and improve cancer outcomes (Austoker et al., 2009; Bankhead, 2017).

To understand the causes for long patient intervals and design effective interventions, researchers have studied how several psychological factors affect patient help-seeking. Reducing time to help-seeking by targeting psychological factors could be especially effective among lower socio-economic groups who are more likely to report psychological barriers, have low symptom knowledge, and present later to a health-care professional (McCutchan, Wood, Edwards, Richards, & Brain, 2015). Factors such as knowledge and interpretation of symptoms and beliefs regarding the curability or fatality of cancer have been suggested to influence the patient interval (McCutchan et

al., 2015; Smith, Pope, & Botha, 2005). For instance, better symptom knowledge has been related to shorter patient intervals in breast (Harirchi, Ghaemmaghami, Karbakhsh, Moghimi, & Mazaherie, 2005; Hunter, Grunfeld, & Ramirez, 2003; Mirfarhadi, Ghanbari, Khalili, & Rahimi, 2017), cervical (Ouasmani et al., 2016), lung (Desalu et al., 2016), and skin cancer (Oliveria et al., 1999). Similarly, attributing experienced symptoms to cancer has been related to shorter patient intervals in colorectal (Jensen, Hvidberg, Pedersen, Aro, & Vedsted, 2016; Simons et al., 2017), breast (Burgess, Ramirez, Richards, & Love, 1998), and head and neck cancers (Akram, Ali Siddiqui, & Masroor Karimi, 2014; Vaisanen et al., 2014). However, not all studies have shown consistent results (Grunfeld & Kohli, 2010; Hashim et al., 2011; Pedersen, Hansen, & Vedsted, 2013; Scott et al., 2008; Scott, McGurk, & Grunfeld, 2008; Smits, Boivin, Menon, & Brain, 2017; van Osch, Lechner, Reubsaet, de Nooijer, & de Vries, 2007).

More positive beliefs about cancer (e.g., that cancer is a treatable disease), have also been related to shorter patient intervals in colorectal (Jensen et al., 2016; Pedersen et al., 2018) and lung cancer (Pedersen et al., 2018). Unfortunately, recent research showed that about 25% of participants from six different countries (UK, Australia, Canada, Denmark, Norway, and Sweden) think that a cancer diagnosis is a death sentence (Pedersen et al., 2018), a belief that does not correspond to many recent improvements in cancer treatment and survival. However, not all studies find a relationship between beliefs and the patient interval (Brain et al., 2014; Grunfeld & Kohli, 2010; Harirchi et al., 2005; Pedersen et al., 2018; van Osch et al., 2007).

The recognition and interpretation of symptoms as cancer-related and beliefs about the treatability of cancer are important components of several health behaviour models used to understand patient help-seeking. For instance, the Judgment to Delay Model (Facione, Miaskowski, Dodd, & Paul, 2002) and the Grounded Model of Breast

Cancer Delay (Unger-Saldana & Infante-Castaneda, 2011) are theories developed in the context of patient help-seeking for cancer symptoms. Both theories consider symptom knowledge, symptom interpretation, and beliefs about the treatability of cancer as important precursors to help-seeking. Another more general model that has been frequently applied to the context of help-seeking for cancer symptoms is the Model of Illness Representation (also referred to as the Common Sense or Self-Regulation Model) (Hunter et al., 2003; Leventhal, 1984; O'mahony & Hegarty, 2009). According to this model, people construct cognitive representations of a disease in order to understand it and cope with it. These cognitive representations form five dimensions, two of which consider the recognition and interpretation of symptoms (identity) and the extent to which the person believes that the disease can be cured (cure/control).

More general models such as the Health Belief Model (Rosenstock, Strecher, & Becker, 1988) and the Theory of Planned Behaviour (Ajzen & Madden, 1986) have also been applied to the context of help-seeking. However, these models were developed to address prevention and behaviour change and their suitability for help-seeking due to symptoms has been questioned (O'mahony & Hegarty, 2009). The Health Belief Model has been frequently used as a basis for interventions to improve cancer awareness and early presentation (Austoker et al., 2009). Within this model, perceived susceptibility (influenced by symptom recognition and interpretation) and perceived severity (influenced by beliefs about the treatability of cancer) motivates individuals to reduce the perceived threat of the disease by taking relevant action (i.e., help-seeking). Perceived susceptibility and severity could also motivate action by influencing attitudes towards help-seeking. Specifically, the Theory of Planned Behaviour considers attitudes and social norms as main determinants of behaviour (Ajzen & Madden, 1986).

The high theoretical relevance of the three psychological factors reviewed above, together with the accumulated number of studies showing mixed results, indicate the need for a systematic synthesis of the evidence. The cancer-site focus of previous reviews and the heterogeneity of study designs and measurement constructs have so far precluded meta-analyses in the context of help-seeking for cancer symptoms (McCutchan et al., 2015). However, the three factors of interest for the current research are frequently measured in diverse studies suggesting they may be universal factors of interest across most cancers. A quantitative synthesis of the literature with respect to such factors would help estimate the strength of relationships and explain the existing heterogeneity by testing potential moderators such as study and sample characteristics. This could reveal the reasons for inconsistent findings and potentially pinpoint to what extent and under what conditions it may be effective to target different psychological factors.

In sum, we conducted a meta-analysis of the relationship between the patient interval and symptom knowledge, symptom interpretation, and beliefs about cancer. These factors are potentially universal (i.e., could be important regardless of the health system or cancer site), actionable (i.e., can be addressed by individual or community campaigns), and considered by various health behaviour theories as determinants of help-seeking for cancer symptoms. A preliminary review indicated that these factors are among the most frequently reported across studies of different cancer sites and definitions and measures are relatively homogenous, thus a meta-analytic synthesis of the literature would be feasible and meaningful.

Methods

Pre-selection of psychological factors for meta-analysis. Several methodological requirements must be met for meta-analysis to be meaningful. These

include having enough studies to reliably estimate an effect size and ideally investigate potential moderators, and sufficient homogeneity between study measures. To identify psychological factors meeting such requirements we conducted a preliminary literature study of the results of several existing systematic reviews, following Kummer, Walter, Chilcot, and Scott (2017). These included the most recent broad-scope systematic review of factors related to help-seeking for cancer symptoms across diverse cancer sites (McCutchan et al., 2015), complemented with several other recent reviews (Balasooriya-Smeekens, Walter, & Scott, 2015; Dubayova et al., 2010; Kummer et al., 2017; Macleod, Mitchell, Burgess, Macdonald, & Ramirez, 2009; Webber, Jiang, Grunfeld, & Groome, 2017). We aimed to identify factors: a) that are psychological, i.e., related to patients' perceptions, interpretations, feelings, or cognitions, b) that are frequently measured in quantitative studies in relation to help-seeking (i.e.,, preliminary identification of at least about 10 studies), c) whose definitions and measures are relatively homogenous, and d) that were not covered by a recent meta-analysis (or an attempt to perform one). Symptom knowledge, symptom interpretation (as cancer vs. other), and beliefs about cancer (i.e., specifically the positive-negative dimension regarding perceived treatability/survivability) met these conditions. Negative emotions such as fear or worry were also frequently cited but were covered by a recent review which determined meta-analysis not to be feasible at this point (Balasooriya-Smeekens et al., 2015).

Literature search. To conduct the three meta-analyses we followed the PRISMA guidelines for conducting and reporting systematic reviews (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009). We searched the following databases: Medline (PubMed), PsychINFO, Web of Science, and Scopus, and considered articles published from 1990 until April 2019 when the search was conducted. The search terms

used are provided in the pre-registration protocol on PROSPERO [CRD42018088944]: tinyurl.com/PatientIntervalR and on the Open Science Framework: osf.io/95cvf/. The list of terms was constructed based on a preliminary review of the literature and the search terms of a recent review of broader scope (McCutchan et al., 2015), and was further expanded after feedback from reviewers.

Selection criteria. We considered quantitative studies with adult participants, including all cancer sites, without restrictions regarding study type. In particular, we considered observational studies that were a) actual symptom presentation studies, i.e., studies with cancer patients or symptomatic patients undergoing investigation for cancer reporting retrospectively how long they waited before seeking help, and b) anticipated symptom presentation studies, i.e., hypothetical cross-sectional studies with healthy populations reporting how long they would wait before seeking help. We included studies reporting the relationship between the patient interval and a) symptom knowledge, b) symptom interpretation as related to cancer, or c) beliefs about the survivability/treatability of cancer. Patient interval was defined as the time in days, weeks or months elapsed between the start of symptoms and the first (actual or hypothetical) medical consultation (Weller et al., 2012). Symptom knowledge referred to the knowledge or recognition of cancer symptoms or warning signs. Symptom interpretation referred to attributing experienced symptoms possibly to cancer or thinking that it could be cancer at some point. Beliefs about cancer referred to beliefs that the participant holds regarding the curability or survivability of cancer, the effectiveness of modern cancer treatments, or the benefits of early diagnosis or treatment. There were no restrictions regarding language. Reviews, qualitative studies, editorials, case reports, and conference abstracts were excluded.

The titles of all studies retrieved were screened by one author who discarded studies if it was clear from the title that they would not meet the inclusion criteria (e.g., systematic reviews or a topic irrelevant to the search). The abstracts of the selected titles were screened for eligibility independently by two researchers; disagreements were resolved through discussion or review of the full text. The full texts of the selected abstracts were reviewed for eligibility by two authors; disagreements were resolved through discussion. Additional search was conducted of the reference lists of the selected studies and the same procedure was followed with the additionally identified titles. Study authors were contacted to provide additional information where needed.

Data extraction. One researcher extracted data from the studies using predefined data fields according to the review protocol and another author checked it thoroughly. Disagreements were resolved through discussion. We extracted basic information about the study, demographic information about participants, a brief description of the study sample (see Table 1), and information regarding several candidate moderators of the studied effects (see below). We also recorded the types of scales used to assess the constructs of interest, their interpretation, and the statistical result reported.

Because the resulting sample of studies was highly international, in addition to the pre-defined list of candidate moderators in the protocol, we extracted several socio-economic country-level indicators that could explain heterogeneity in the observed effects. We considered the country where each study was conducted and extracted the corresponding Human Development Index (HDI), GINI coefficient, and health expenditure in thousands of $USD three years before the article's date of publication (e.g., for 2000 for a study published in 2003) or for the nearest year when data were not available. Data were obtained from the data bank of the World Bank

(http://databank.worldbank.org). The HDI is a summary measure of average achievement in key dimensions of human development including a long and healthy life, being knowledgeable (e.g., mean years of schooling), and having a decent standard of living (Malik, 2013). The GINI coefficient is a measure of the country's income inequality (0=perfect equality to 100=perfect inequality). Health expenditure was computed based on the country's GDP and the percentage of GDP dedicated to public health expenditure.

Risk of bias assessment. The risk of bias for each study was assessed with the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies checklist (National Institutes of Health, 2014), which is suitable for cross-sectional descriptive studies. The scale was adapted by dropping five items applicable to cohort studies (e.g., loss to follow up, exposure measured prior to outcome). In addition, three items assessing the quality of the patient interval measurement were added from the Aarhus statement checklist (Weller et al., 2012). These items referred to a) the timing of the interview in relation to the date of diagnosis, b) triangulation of self-reported data with other sources, and c) treatment of the patient interval in analysis. Items a) and b) apply only to studies with patients already diagnosed with cancer; other types of studies received a score of 1 for these items as they are not susceptible to such biases. Thus, the maximum possible score on the quality assessment was 12 (9 NIH items + 3 Aarhus items). We used this score in analyses and for descriptive purposes considered a score higher than 80% (10 or more) as low risk of bias, a score of 60% to 80% (>7 and <10) as medium risk, and a score lower than 60% (≤7) as high risk. These cut-offs were arbitrary and a broader range of scores was considered as high risk given the low evidence category of the studies (cross-sectional). Studies were assessed independently by two researchers and disagreements were resolved through discussion.

Statistical analysis. The majority of studies (35, 72%) analyzed the patient interval by dichotomizing it into "delay" vs. "no delay" groups, and the most frequently reported effect size measure was the odds ratio (OR): for one unit change in the symptom knowledge score (reflecting the knowledge of one additional symptom), for attributing a symptom to cancer vs. to other causes, and for one unit change in the cancer belief scale used. Effect sizes that were not originally ORs were transformed to ORs with the associated 95% confidence intervals (CI) using formulae for effect size transformation (e.g., to transform standardized mean differences into ORs (da Costa et al., 2012; Hozo, Djulbegovic, & Hozo, 2005; Peterson & Brown, 2005; Polanin & Snilstveit, 2016; Rodríguez-Barranco, Tobías, Redondo, Molina-Portillo, & Sánchez, 2017). The implications of these transformations were examined in sensitivity analysis (see below).

Some studies (Ouasmani et al., 2016; Pedersen et al., 2018; Quaife et al., 2014) reported more than one effect size for a particular relationship of interest in the same sample of participants (based on separate analyses for several cancer symptoms). Because of the assumption of independence of meta-analysis, only one effect size can be considered per study sample for a given relationship; thus, we estimated an average effect size across cancer symptoms whereby effect sizes were weighed by the inverse of the sampling variances (Viechtbauer, 2010).

Analyses were conducted in R using the package metaphor (Viechtbauer, 2010). Meta-analyses were conducted using logORs and studies were weighed by their precision using standard errors (Viechtbauer, 2010). Random-effects models were fitted because substantial heterogeneity between studies was expected. Confidence intervals (95%) excluding 0 were considered as significant and the I^2 statistic was used as a measure of heterogeneity. Models were estimated separately for studies with healthy

populations and studies with patients. We tested the following candidate moderators: definition of delay, risk of bias score, effect based on adjusted vs. unadjusted (for other covariates) analysis, gender composition of the sample (female vs. mixed), and use of theoretical model vs. not. Definition of delay was expressed in weeks and referred to the scale used to measure the patient interval (e.g., when a study divided the sample into "delay" and "no delay" groups based on the cut-off of one month, the value of the variable was 4 weeks). The moderators were tested one at a time due to the limited number of studies. An OR<1 for the effect of a moderator means that the presence/higher value of the moderator is associated with a stronger effect; an OR>1 for the effect of a moderator means that the presence/higher value of the moderator is associated with a weaker effect. Because of the low frequency of studies on separate cancer sites per-site synthesis was not meaningful; however, data are grouped according to cancer site in figures and are openly available for researchers interested in specific locations (on the Open Science Framework: osf.io/95cvf/).

Sensitivity analyses involved i) effect size estimation excluding studies that were outliers (based on standardized residuals and influential case diagnostics using Cook's distances, (Viechtbauer, 2010)), ii) excluding studies with high risk of bias, and iii) comparing effect sizes between studies where those were transformed from other measures (not original ORs) to those where effect sizes were originally ORs (Polanin & Snilstveit, 2016). The possibility of publication bias was examined using i) contour enhanced funnel plots that can differentiate asymmetry due to publication bias from that due to other factors (Peters, Sutton, Jones, Abrams, & Rushton, 2008) and ii) Beg and Egger statistical tests (Viechtbauer, 2010). In a final exploratory ecological analysis country indicators were tested as moderators of the documented relationships.

Results

Figure 1 shows a flow chart of the study selection process and Table 1 presents the main characteristics of the included studies. The final sample consisted of 47 studies, of which 31, 15, and 18 assessed the relationship of patient interval with symptom knowledge, symptom interpretation, and cancer beliefs, respectively. The studies totalled 44,961 participants of whom 28,497 (63%) were women. The majority of studies (70%) focused on specific cancer sites, including the breast (30%), colon/rectum (11%), head or neck (11%), ovaries (6%), skin (4%), cervix (4%), and lung (4%). The remaining studies (30%) focused on multiple cancer sites. The studies were conducted in 22 different countries, including both higher and lower income countries, with most representation of the United Kingdom (28%), USA (9%), the Netherlands (6%), Denmark (7%), and India (6%).

There were more studies with patients (k=26, 55%) than with healthy populations (k=21, 45%). Compared to patient studies that had an average sample size of M=220 (min=34, max=513), healthy population studies had larger sample sizes (M=1868, min=238, max=6965), with 15 (71%) using some form of representative or random sampling of the population. Six of the 26 patient studies were conducted on symptomatic patients who had not yet received a diagnosis; the remaining studies included patients with a confirmed cancer diagnosis.

Only 23% of the studies were informed by a theoretical model regarding what factors could affect help-seeking (see Table 1 for the specific theoretical models used). Three studies (6%) received a high risk of bias rating; 24 (51%) received a low risk of bias rating and 20 (43%) medium/uncertain. Funnel plot results and statistical tests did not indicate publication bias and are included as Supplementary Materials. Detailed results of all analyses reported below are also available as Supplementary Materials.

Symptom knowledge (k=31)

Instruments used to measure symptom knowledge included the Cancer Awareness Measure (CAM) (Brain et al., 2014; Desalu et al., 2016; Robb et al., 2009; Smits et al., 2017; Waller et al., 2009), the Awareness and Beliefs about Cancer (ABC) measure (Donnelly et al., 2017), the Knowledge of Cancer Warning Signs Inventory (KCWSI) (de Nooijer, Lechner, & de Vries, 2002; de Nooijer, Lechner, & De Vries, 2003; van Osch et al., 2007), the Identity subscale of the Illness Perception Questionnaire (IPQ)(Grunfeld & Kohli, 2010; Hunter et al., 2003), and other diverse scales, including self-generated items. All but one study measured objective symptom knowledge (correct vs. incorrect recognition of symptoms as potentially indicative of cancer); the remaining study measured self-reported symptom knowledge before diagnosis (Lim et al., 2014).

Healthy population studies (k=19, N=37,298). Identifying more symptoms of cancer was on average related to a shorter patient interval: OR=.73, 95% CI [.63, .84], but the effects were highly heterogeneous, I^2=90% (see Figure 2). There was one significant moderator that reduced this heterogeneity: Studies with mixed gender composition found larger effects compared to studies with females only, OR=.66, 95% CI [.52, .83], I^2=83%. Figure 2 shows that there was a group of studies focused on breast or ovarian cancer in females that that reported smaller or non-significant effects and were driving this moderation effect. Sensitivity analyses showed that effects sizes that were originally ORs were not significantly different from those that were not originally ORs; there were no outliers and no studies at high risk of bias in this analysis (details in Supplementary Materials).

Patient studies (k=12, N=2,908). Identifying more symptoms of cancer was related to a shorter patient interval: OR=.40, 95% CI [.23, .69], and effects were highly heterogeneous, I^2=93% (see Figure 3). This effect was larger and less precise than that

found in healthy population studies. There was one significant moderator: Studies that defined a larger period as a threshold for delay found stronger effects, OR=.85, 95% CI [.78, .93] (OR for one week change in the definition of delay), I^2=85%. Sensitivity analysis showed that there was one outlier (Ouasmani et al., 2016): the pooled effect without it was OR=.62, 95% CI [.50, .76], I^2=42%, and there was one study at high risk of bias (Harirchi et al., 2005): the pooled effect without it was OR=.43, 95% CI [.24, .74], I^2=94%; there was only one study for which the original effect size was not OR (details in Supplementary Materials).

Symptom interpretation (k=15)

All studies used self-generated items to assess symptom interpretation. There were only two healthy population studies: one based on a scenario about colorectal cancer symptoms with N=1,088 (Simons et al., 2017) and another about lung cancer symptoms with N=848 (Tustin, 2012). Both studies showed that participants who correctly suspected cancer as a potential cause for the symptoms described in a vignette would seek medical help more quickly than patients who made an incorrect attribution of the symptoms. The remaining studies were retrospective, ten with patients with a confirmed cancer diagnosis and three with patients under investigation (Dent et al., 1990; Li et al., 2012; Scott et al., 2008).

Patient studies (k=13, N=2,239). Attributing symptoms to cancer was related to a shorter patient interval, OR=.52, 95% CI [.36, .75], I^2=69% (see Figure 4). None of the candidate moderators were significant. Sensitivity analyses showed that effects sizes that were originally ORs were not significantly different from those that were not originally ORs and there were no outliers. There were two studies at high risk of bias in this analysis (Andersen & Cacioppo, 1995; Panzarella et al., 2014), the pooled effect

without them was OR=.58, 95% CI [.41, .83], I^2=64% (details in Supplementary Materials).

Cancer beliefs (k=18)

Two studies measured beliefs that cancer is deadly vs. treatable (fatalistic beliefs) (Gullatte, Brawley, Kinney, Powe, & Mooney, 2010; Kakagia et al., 2013). The remaining studies measured beliefs about the curability of cancer or the benefits of early detection and treatment. Among the scales used were the Awareness and Beliefs about Cancer (ABC) measure (Donnelly et al., 2017), items from the Cure/control subscale from the Illness Perception Questionnaire (Grunfeld & Kohli, 2010; Hunter et al., 2003; Jensen et al., 2016), the Power Fatalism Inventory (Gullatte et al., 2010), and self-generated items. For the purpose of analyses, the results were expressed such that a higher score reflected more positive beliefs (one-point change in the used scale).

Healthy population studies (k=11, N=22,214). More positive beliefs about cancer were related to a shorter patient interval, OR=.70, 95% CI [.52, .92], I^2=84% (Figure 5). Three moderators explained heterogeneity of the effects: studies in which the effect was not adjusted for other covariates reported larger effect sizes, OR=.54, 95% CI [.33, .90], I^2=74%, and so did studies with higher risk of bias (i.e., lower quality score), OR=.69, 95% CI [.52, .91], I^2=72%. Studies that were based on a theoretical model reported smaller effects, OR=2.08, 95% CI [1.38, 3.10], I^2=61%. Again, there was a small group of studies on breast and ovarian cancer in females reporting non-significant relationships that contributed to these moderation effects (see Figure 5). Sensitivity analyses showed that studies where the original effect sizes were not ORs (which was the case for the studies on breast and ovarian cancer) found smaller effects; there were no outliers or high risk studies in this sample (details in Supplementary Materials).

Patient studies (k=7, N=1,836). More positive beliefs about cancer were related to a shorter patient interval, OR=.51, 95% CI [.32, .82], I^2=83% (Figure 6). Similar to results with symptom knowledge, this effect was larger and less precise than that found in studies with healthy populations. One moderator explained heterogeneity of the effects: studies with mixed gender composition found larger effects compared to studies with females only (these were again studies on breast cancer), OR=.39, 95% CI [.20, .73], I^2=56%. Sensitivity analyses showed that effects sizes that were originally ORs were not significantly different from those that were not originally ORs; neither were those from studies that measured fatalistic beliefs compared to the rest; there were no outliers in this analysis but there was one high risk study (Harirchi et al., 2005). The pooled effect without it was: OR=.49, 95% CI [.29, .85], I^2=86%.

Country indicators

The exploratory analysis with the obtained country indicators showed that the GINI coefficient was related to the effects of symptom knowledge and interpretation. In particular, higher income inequality was related to stronger protective effects of symptom knowledge, $OR_{\text{high vs. low inequality}}$=.60, 95% CI [.39, .92] and symptom interpretation as related to cancer, $OR_{\text{high vs. low inequality}}$=.51, 95% CI [.30, .89] (details in Supplementary Materials). Figure 7 illustrates that studies in countries with higher income inequality tended to find larger effects of symptom knowledge (reflected by a smaller OR). The other indicators showed no significant effects.

Discussion

The patient interval is one of the most important factors contributing to diagnostic delays, ultimately affecting patient outcomes. To our knowledge, this is the first systematic review to offer a quantitative synthesis of studies investigating the

relationship between several psychological factors and the patient interval. Our review covered almost 30 years of research from all over the world. The current results have implications not only for intervention design but also for theory development and methodological practices in the field.

Symptom knowledge

Consistent with previous narrative reviews (Macleod et al., 2009; McCutchan et al., 2015; Smith et al., 2005), we find strong evidence that the correct identification of more cancer symptoms is related to shorter patient intervals, with each additional symptom correctly identified potentially halving the odds of delayed consultation. This relationship was significant both in studies with healthy populations considering consultation for hypothetical symptoms and in studies with patients who actually experienced symptoms and sought medical attention. Obtaining converging evidence across the two types of studies is encouraging given their inherent limitations. Hypothetical studies with healthy populations are limited by the fact that participants are only stating their intentions; intentions are usually strong but far from perfect predictors of actual behavior (Sheeran, 2002). Retrospective patient studies, and estimations of the patient interval in particular, are limited by a variety of memory biases and other issues related to patients' interpretation of bodily sensations as symptoms (Andersen, Vedsted, Olesen, Bro, & Søndergaard, 2009). In addition, patients' knowledge of symptoms may improve as a result of their illness and experience. The latter would imply a weaker or non-existent relationship between knowledge and consultation time in retrospective patient studies; contrary to this expectation, we found a stronger relationship in patient compared to healthy population studies. However, the pooled effects for patient studies were also less precise and were based on a smaller sample of studies with fewer participants.

Symptom interpretation

We also found evidence that attributing an experienced symptom to cancer is related to a shorter patient interval. However, we only located fifteen studies reporting a relationship (only two in a healthy population), and most of them were with patients with breast, colorectal or head and neck cancers. Given the frequently unspecific symptoms of colorectal cancer and the rarity of head and neck cancers, cancer attributions among patients are infrequent, making large sample sizes necessary to establish statistical differences (Balasooriya-Smeekens et al., 2015; Smith et al., 2005). This can explain why many of the individual studies failed to find significant effects.

More research is needed testing the relationship between symptom attribution and time to help-seeking for other more prevalent cancers beyond breast cancer. Finding that attributing symptoms to cancer is related to shorter times to help-seeking may seem like a trivial or unsurprising finding. However, previous research has shown that the idea of cancer is emotion-evoking, and emotions such as fear could act both as a trigger and as a barrier to consultation for symptoms suggestive of cancer (Balasooriya-Smeekens et al., 2015; Smith et al., 2005). This suggests that for certain individuals, thinking that an experienced symptom could be cancer could deter from help-seeking and it is important to investigate this issue further.

Cancer beliefs

Our analyses also revealed that individuals who have more positive beliefs about cancer have shorter patient intervals. In other words, individuals who believe that cancer is treatable (as opposed to fatal) consult more quickly for their symptoms. Similar to symptom knowledge, obtaining corroborating evidence from both healthy population and patient studies speaks to the evidential value of this finding. For instance, studying

the role of beliefs about cancer in patient studies can be problematic because these beliefs can change after hearing their prognosis or learning more about their disease.

As mentioned previously, a substantial proportion of the population has very negative beliefs about cancer (Pedersen et al., 2018) that often do not reflect current advances in the therapeutic treatment of many cancers. Together, the current results suggest that educating patients about cancer symptoms may not be sufficient to promote early diagnosis if fatalistic or negative beliefs about cancer are not addressed. For instance, in a recent study among participants who recognized unexplained bleeding as a potential colorectal cancer symptom, more positive beliefs about cancer were related to a lower probability of delaying consultation; in contrast, among participants who did not recognize this symptom as cancer-related, this relationship was not present (Pedersen et al., 2018). This indicates that symptom knowledge, interpretation, and beliefs can interact in important ways, and hence future studies and theories should consider how these factors interact to motivate help-seeking.

Implications for interventions

The results of this review suggest that both symptom knowledge/interpretation and beliefs about cancer should be addressed in interventions and public campaigns. Whereas most, if not all, interventions aiming to improve early presentation outcomes or increase cancer awareness have provided information about relevant symptoms (Austoker et al., 2009), fewer interventions have directly addressed negative or fatalistic beliefs about the treatability of cancer, or given them a central role in intervention content (see for exceptions: Boundouki, Humphris, & Field, 2004; de Nooijer, Lechner, Candel, & de Vries, 2004; McCullagh, Lewis, & Warlow, 2005). Thus, given the relatively poor success rate of previous interventions (Austoker et al., 2009), this is an important aspect that could lead to improvement.

At the same time, public campaigns should be designed considering potential challenges to reduce times to help-seeking. For instance, recent "Be Clear on Cancer" campaigns in England have addressed both symptom recognition and the better treatability of symptomatic cancer through early detection (Bethune et al., 2013; Hughes-Hallett, Browne, Mensah, Vale, & Mayer, 2016). Although such campaigns have generally contributed to increased awareness (Power & Wardle, 2015), effects on specialist referrals have been short-lived and no associated increases in cancer diagnoses have been observed (Bethune et al., 2013; Hughes-Hallett et al., 2016). This suggests that, among others, the campaigns may have reached the "worried well" (Hughes-Hallett et al., 2016) but may not have had the desired effect on the individuals in need. For instance, individuals with lower literacy and socio-economic background often have lower symptom knowledge and more fatalistic beliefs about cancer, and tend to search less for health information (Emanuel, Godinho, Steinman, & Updegraff, 2018; Kobayashi & Smith, 2016; McCutchan et al., 2015). Future research should examine ways to reach such individuals, and overcome barriers to the effectiveness of campaigns addressing key psychological factors.

Besides general recommendations, this review also offers an overview of the available evidence regarding the relationships of interest for distinct cancer sites for practitioners who may be interested in designing site-specific studies or interventions. It also suggests that evidence from skin, lung, cervical, and ovarian cancer remains relatively scarce and thus more research is needed to investigate the relationships between the patient interval and symptom knowledge, interpretation, and cancer beliefs for these cancer sites. In contrast, more studies on breast cancer are available but the findings have been rather mixed.

Finally, the exploratory ecological analysis demonstrated that symptom knowledge and attribution of symptoms to cancer showed a stronger protective relationship in studies from countries with larger income inequality. One interpretation of this finding has to do with the accessibility of healthcare services. In countries where healthcare is relatively accessible for everyone, the knowledge that a symptom could be indicative of cancer may be less determinant of consultation time. Patients in such countries may generally consult for their symptoms regardless of their knowledge or appraisal of symptoms. In contrast, in countries where healthcare is less accessible to the more economically disadvantaged, recognition of symptoms as potentially indicative of cancer could be an important push factor for patients to seek consultation despite the experienced barriers. This finding, together with results showing that individuals of lower socio-economic status have lower knowledge of cancer (Macleod et al., 2009; McCutchan et al., 2015), speaks of the potentially higher utility of interventions targeting more vulnerable individuals or societal groups. However, these findings are only suggestive and should be further explored in future research.

The role of theoretical models

Overall, only one quarter of the included studies were informed by theoretical models of factors that could influence the patient interval (see Table 1). This demonstrates that the study of help-seeking for cancer symptoms is still largely empirically and not theoretically driven. This could be because a large number of studies were conducted by clinicians who are generally unfamiliar with health behavior models and their utility in explaining help-seeking. Many of the included studies that were theoretically driven used the Model of Illness Representation (also referred to as the Common Sense or Self-Regulation Model) (Hunter et al., 2003; Leventhal, 1984; O'Mahony & Hegarty, 2009). This model, although not designed specifically for the

context of help-seeking for cancer symptoms, can be useful for the purpose because it addresses people's responses to and coping with symptoms. Other more general theoretical models such as the Health Behaviour Model (Rosenstock et al., 1988) and the Theory of Planned Behaviour (Ajzen & Madden, 1986) were also used but may be less suitable because they were initially developed for the context of preventive behaviour and not for responses to symptoms or illness (O'Mahony & Hegarty, 2009). The fact that these models do not directly incorporate the role of symptom knowledge, interpretation, and cancer beliefs – factors shown to be important drivers of help-seeking in the current review– supports this position.

Finally, there are at least two theoretical models specifically developed to explain and predict help-seeking for cancer symptoms that did not find their way into the articles part of this review: the Judgment to Delay Model (Facione et al., 2002) and the Grounded Model of Breast Cancer Delay (Unger-Saldana & Infante-Castaneda, 2011). Both of these models have been developed for breast cancer, thus, their generalizability to responses to symptoms other than breast symptoms is not clear. Overall, there seems to be a need for a general theoretical model of help-seeking for cancer symptoms that could be applied to diverse cancer sites. The current work shows that symptom knowledge, interpretation, and beliefs about the treatability of cancer are related to help-seeking and should thus be among the prominent constructs in such a model.

Study heterogeneity and recommendations for methodological practices

Across several analyses, we identified a group of studies reporting insignificant effects: what these studies had in common was that they were about breast or ovarian cancer, based on a theoretical model, or reporting effects adjusted for covariates. At this point, however, we cannot conclude that symptom knowledge and cancer beliefs have

no effect on help seeking for symptoms of breast or ovarian cancer because many of the studies that were focused on various cancers included these cancers, too. Instead, the lack of effects may be due to the use of theoretical models that measure or adjust for other more proximal predictors of help-seeking that may mediate the effects of knowledge and beliefs. For instance, many of the aforementioned studies measured and/or controlled for in the analyses for constructs such as perceived benefits or barriers to help-seeking, attitudes, or behavioral intentions (de Nooijer et al., 2003; Grunfeld & Kohli, 2010; Scott et al., 2008; Smits et al., 2017). If these variables mediate the effects of knowledge and beliefs on help-seeking, then their inclusion would render the effects of knowledge and beliefs insignificant.

Overall, there was considerable heterogeneity across studies, which was expected because we combined evidence from multiple cancer locations and 22 countries. The heterogeneity expressed with I^2 was between 50% and 90%. Hence, the estimates from our models are only broadly indicative of the underlying true effect sizes.[1]

Some of the heterogeneity was due to practices that were arbitrary and that should be homogenized. The Aarhus statement, which is the primary reference on methodology of early cancer diagnosis research, addressed many important issues regarding design and reporting; however, analytical procedures were not addressed in detail (Weller et al., 2012). In the studies selected for the current review, the most common analytical practice was to dichotomize the patient interval into ‘delayed” vs. “not delayed” groups. This was based on a) guidelines regarding how soon patients

[1]Whereas such high heterogeneity is common in meta-analyses aiming to answer broader questions, it is important that it be properly addressed and discussed (Schroll, Moustgaard, & Gøtzsche, 2011). On one hand, the OR is highly sensitive to variation in the base event rate (e.g., the proportion of patients with long help-seeking intervals among those who do not think of cancer), which was highly variable across studies and could explain some of the variation in effect sizes (Green & Higgins, 2005). On the other hand, the I^2 statistic tends towards 100% for meta-analyses based on studies with large sample sizes (Li et al., 2015; Rücker, Schwarzer, Carpenter, & Schumacher, 2008), as was the case in the current research, so it is not a fully reliable measure of variability between studies.

should seek attention in healthy population studies, b) an arbitrary number of months in patient studies, which varied substantially, or c) a data-driven reason such as median split in both types of designs. Reducing existing variance in analytical practices would be an important step to study factors related to the patient interval more effectively. This could be achieved by establishing common guidelines that either recommend one good-reasoned cut-off for each cancer site or encourage data transformation instead of dichotomization in the case of skewed data.

Finally, one limitation of this review and research area in general is the low evidence level. We assessed the risk of bias of each study but this assessment was relative rather than absolute, because all studies were of low evidence category (cross-sectional). Based on the results we found no indications of publication bias and given the nature of the studies reviewed (e.g., multiple measures, non-experimental and descriptive) we find it unlikely that lack of positive results could have resulted in substantial publication bias.

Conclusions

Our meta-analysis points to three potentially universal predictors of help-seeking for cancer symptoms, namely symptom knowledge, symptom interpretation as cancer-related, and beliefs about the treatability of cancer. These factors were related to consultation times of participants from different countries and across diverse cancer sites. The psychological factors studied in this review are actionable – they can be addressed in individual interventions or community information campaigns. Whereas almost all interventions aiming to promote early presentation contain information about symptom knowledge, fewer interventions have directly addressed negative beliefs about cancer such as fatalism (Austoker et al., 2009; Power & Wardle, 2015). The current results support the idea that interventions should aim not only to raise awareness of the

warning signs of cancer, but also give more central role to its treatability. This is particularly important among more socio-economically vulnerable groups who tend to have lower symptom knowledge and more negative beliefs about cancer. Symptom knowledge, symptom interpretation, and beliefs about the treatability of cancer should be considered as determinants of the patient interval in theoretical models aiming to explain patient help-seeking behavior for potential cancer symptoms.

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Figure captions

Figure 1. Flow chart of the study selection process.

Figure 2. Forest plot of the meta-analysis of the relationship between symptom knowledge and patient interval in studies with healthy population (k=19, N=37,298).

Note: The displayed measure is log odds ratio, where lower negative values indicate a stronger protective relationship of symptom knowledge on the patient interval. LLCI/ULCI=Lower/Upper level 95% confidence interval. Cancer: B=breast, OV=ovarian, L=lung, VAR=various. Gender=gender composition of the sample.

Figure 3. Forest plot of the meta-analysis of the relationship between symptom knowledge and patient interval in studies with patients (k=12, N=2,908).

Note: The displayed measure is log odds ratio, where lower negative values indicate a stronger protective relationship of symptom knowledge on the patient interval. LLCI/ULCI=Lower/Upper level 95% confidence interval. Cancer: B=breast, CER=cervical, CL=colorectal, HN=head and neck cancer, SK=skin.

Figure 4. Forest plot of the meta-analysis of the relationship between symptom interpretation (attribution to cancer vs. not) and patient interval in studies with patients (k=13, N=2,239).

Note: The displayed measure is log odds ratio, where lower negative values indicate a stronger protective relationship between symptom attribution to cancer on the patient interval. LLCI/ULCI=Lower/Upper level 95% confidence interval. Cancer: B=breast, CL=colorectal, HN= head and neck cancer, VAR=various.

Figure 5. Forest plot of the meta-analysis of the relationship between cancer beliefs and patient interval in studies with healthy population (k=11, N=22,214).

Note: The displayed measure is log odds ratio, where lower negative values indicate a stronger protective relationship of positive beliefs (e.g., that cancer is treatable) on the patient interval. LLCI/ULCI=Lower/Upper level 95% confidence interval. Cancer: B=breast, OV=ovarian, VAR=various. Adj. effect=whether the effect was adjusted for covariates or not. Theory=whether the article was based on a theoretical model of factors influencing the patient interval or not.

Figure 6. Forest plot of the meta-analysis of the relationship between cancer beliefs and patient interval in studies with patients (k=7, N=1,836).

Note: The displayed measure is log odds ratio, where lower negative values indicate a stronger protective relationship of positive beliefs (e.g., that cancer is treatable) on the patient interval. LLCI/ULCI=Lower/Upper level 95% confidence interval. Cancer: B=breast, CL=colorectal, SK=skin, VAR=various. Gender=gender composition of the sample.

Figure 7. Relationship between income inequality (expressed by the GINI coefficient, where higher values indicate greater inequality) and the effect size for the relationship between symptoms knowledge and the patient interval. Countries with higher income inequality tend to find stronger effects (indicated by lower ORs).

Note: The two studies from South Africa (outlier on the GINI coefficient) are not included in the figure, k=28

Table 1. Basic characteristics of the included studies ordered according to publication date.
Note: K=knowledge, I=interpretation, B=beliefs. N=sample size.

First author (Full reference)	Pub. year	Cancer site	Country	Population	Theoretical model of factors influencing patient help-seeking	Brief description of the sample population	N	Average age	% females	Risk of bias (points on assessment)	Measures
Dent (Dent et al., 1990)	1990	colorectal	Australia	patients	none	Patients aged 35 years and older presenting with a new rectal bleeding episode, interviewed before definitive diagnosis had been made.	93	55	46	Medium (8)	I
Andersen (Study 1) (Andersen & Cacioppo, 1995)	1995	various (gynaecological: cervix, endometrium, vulva, ovary, vagina)	USA	patients	Psychophysiological comparison theory	Women diagnosed with gynaecological cancer, between 24 to 75 years.	34	20	100	High(7)	I
Burgess (Burgess, Ramirez, Richards, & Love, 1998)	1998	breast	United Kingdom	patients	none	Women diagnosed with invasive breast cancer aged below 60 (n = 132) and 60 or over (n = 53).	185	54	100	Low (11)	I
Oliveria (Oliveria et al., 1999)	1999	skin	USA	patients	none	Patients newly diagnosed with melanoma of 18 years or older	255	majority are below 60	45	Medium (9)	K
Thongsukai (Thongsuksai, Chongsuvivatwong, & Sriplung, 2000)	2000	breast	Thailand	patients	none	Patients with histologically confirmed invasive carcinoma	94	55	100	Low (12)	I, B

						of the breast who were admitted to the hospital for initial treatment.					
de Nooijer (de Nooijer, Lechner, & de Vries, 2002)	2002	various	Netherlands	healthy population	none	Adults who volunteered to participate, recruited by newspapers, aged 18 years or older.	1530	46	80	Low (10)	K
Hunter (Hunter, Grunfeld, & Ramirez, 2003)	2003	breast	United Kingdom	healthy population	Self-regulation model; Theory of planned behaviour	A general population sample, representative of the UK, aged between 16 and 86.	546	47	100	Medium (9)	K, B
de Nooijer (de Nooijer, Lechner, & De Vries, 2003)	2003	various (cancer warning signs)	Netherlands	healthy population	Theory of planned behaviour	Convenience sample of asymptomatic Dutch adults without cancer recruited via newspapers.	475	47	77	Low (10)	K
Harirchi (Harirchi, Ghaemmaghami, Karbakhsh, Moghimi, & Mazaherie, 2005)	2005	breast	Iran	patients	none	Women with a histologically proven diagnosis of advanced breast cancer who presented to a university hospital, aged 20 to 79.	200	47	100	High (5)	K, B
Burgess (Burgess et al., 2006)	2006	breast	UK	patients	none	Women 65 or over with any stage of newly diagnosed breast cancer.	69	78	100	Low (10)	I
van Osch (van Osch,	20	various (cancer	Netherla	healthy populati	The I-change	Dutch adults 55	45	69	51	Medium	K, B

Lechner, Reubsaet, de Nooijer, & de Vries, 2007)	07	warning signs)	nds	on	model	years or older.	9			(9)	
Scott (Scott, McGurk, & Grunfeld, 2008)	20 08	head/neck	United Kingdo m	patients	the Self-regulation model	Newly referred patients 18 years or older with potentially malignant oral symptoms.	80	53	70	Medium (9)	K, I
Waller (Waller et al., 2009)	20 09	various (cancer warning signs)	United Kingdo m	healthy populati on	none	Representa tive sample of the UK ethnic minority population s (Indian, Pakistani, Banglades hi, Caribbean, African, and Chinese), aged 18 or over.	15 00	35-40	50	Low (10)	K
Robb (Robb et al., 2009)	20 09	various (cancer warning signs)	United Kingdo m	healthy populati on	none	Representa tive sample of UK adults, recruited through the Office for National Statistics, 16 years and over.	22 08	aroun d 45	56	Low (10)	K
Grunfeld (Grunfeld & Kohli, 2010)	20 10	breast	India	healthy populati on	Self-regulation model; Theory of planned behavior	Convenien ce samples of women aged 16 to 85 years, recruited in Hindu religious festival and non-Hindy districts, without personal history of breast cancer.	68 5	49	100	Low (11)	K, B
Gullatte (Gullatte, Brawley, Kinney, Powe, & Mooney, 2010)	20 10	breast	USA	patients	none	African American women 30 years or older (range: 30-84) diagnosed	12 9	54	100	Medium(9)	B

						with breast cancer within the last year, recruited from medical clinics.					
Bhosai (Bhosai, Sinthusake, Miwa, & Bradley, 2011)	2011	various (beast, cervical colorectal, lung, thyroid, other)	Thailand	patients	none	Cancer patients undergoing treatment, aged 20 or over.	264	around 50 or more	68	Medium (9)	B
Hashim (Hashim et al., 2011)	2011	colorectal	Malaysia	patients	none	Patients aged 41 to 86 with rectal bleeding and who had agreed for colonoscopy, not yet diagnosed.	80	61	" The majority are male. "	Medium (9)	K
Li (Li et al., 2012)	2012	breast	China	patients	none	Women seeking evaluation for self-identified breast symptoms.	425	52	100	Low (11)	I
Tustin (Tustin, 2012)	2012	lung	USA	healthy population	Conceptual framework based on several theoretical models	Adults 18 years or older drawn from the general American population.	848	54	51	Low (11)	I
Pedersen (Pedersen, Hansen, & Vedsted, 2013)	2013	colorectal	Denmark	patients	none	Incident colorectal cancer cases (new diagnosis excluding recurrent cancers), aged 18 or over.	136	68	45	Medium(9)	I
Kakagia (Kakagia et al., 2013)	2013	skin	Greece	patients	none	Patients with cutaneous squamous cell carcinoma at first examination to be followed by surgery, aged between	513	64,3	43	Low (10)	B

						46 and 87.					
O'Mahony (O'Mahony, McCarthy, Corcoran, & Hegarty, 2013)	2013	breast	Ireland	patients	Conceptual framework based on several theoretical models	Women 18 years or older with self-discovered breast symptoms during first visit to a breast clinic, aged from 18 to 80 years.	449	85% are under 50	100	Medium (9)	K
Panzarella (Panzarella et al., 2014)	2013	head/neck	Italy	patients	none	Patients with histological diagnosis of squamous cell carcinoma awaiting treatment, aged 32-92.	156	62	29	High(7)	I
Lim (Lim et al., 2014)	2014	cervical	United Kingdom	patients	none	Females aged 18-29 years diagnosed with cervical cancer, recruited through hospitals and charity websites. Subselection of patients diagnosed via symptomatic presentation.	40		100	Medium (9)	K
Vaisanen (Vaisanen et al., 2014)	2014	head/neck	Finland	patients	none	Patients in whom head or neck cancer was diagnosed, first visit after verification of disease, aged 30 to 89.	85	62	36	Medium (8)	I
Brain (Brain et al., 2014)	2014	ovarian	United Kingdom	healthy population	none	Women aged 50 years or older without	1043	65	100	Low (10)	K, B

						diagnosis of ovarian cancer or oophorectomy, random probability sampling.					
Akram (Akram, Ali Siddiqui, & Masroor Karimi, 2014)	2014	head/neck	India	patients	none	Patients newly diagnosed and previously untreated for squamous cell carcinoma of the oral cavity and oropgarynx.	259	56% below 50	8	Low (10)	K, I
Quaife (Quaife et al., 2014)	2014	various (breast, colorectal, lung)	United Kingdom	healthy population	none	Adults aged 50 or more, recruited through random probability sampling.	6965	65	62	Low (10)	K
Ouasmani (Ouasmani et al., 2016)	2016	cervical	Morocco	patients	none	Women who had started their treatment for cervical cancer, aged between 28 to 83.	401	52	100	Low (10)	K
Desalu (Desalu et al., 2016)	2016	lung	Nigeria	healthy population	none	Adults 18 years or older recruited using stratified sampling.	1125	33	49	Low (11)	K
Jensen (Jensen, Hvidberg, Pedersen, Aro, & Vedsted, 2016)	2016	colorectal	Denmark	patients	Common Sense Model (Self-regulation Model)	Patients registered with histologically confirmed colorectal cancer.	436	68	44	Medium (9)	I, B
Agrawal (Agrawal et al., 2016)	2016	head/neck	India	patients	none	Individuals from the general public who reported experiencing a possible oral cancer	226	65% are below 40	19	Medium (9)	K

						symptom in the last 12 months.					
Mirfarhadi (Mirfarhadi, Ghanbari, Khalili, & Rahimi, 2017)	2017	breast	Iran	patients	none	Patients diagnosed with breast cancer referred for checkup.	232	50	100	Medium (9)	K
Simons (Simons et al., 2017)	2017	colorectal	United Kingdom	healthy population	none	Adults registered with general practices, aged between 18 and 96.	1088	between 18 and 96	72	Medium (9)	I
Smits (High Risk sample) (Smits, Boivin, Menon, & Brain, 2017)	2017	ovarian	United Kingdom	healthy population	Health Belief model	Women at high risk of ovarian cancer based on family history or genetic test results, over 30 years.	238	53	100	Medium(9)	K
Smits (Low Risk sample) (Smits et al., 2017)	2017	ovarian	United Kingdom	healthy population	Health Belief model	Women from the general population (Wales), above 50, recruited using random probability sampling.	1043	65	100	Medium(8)	K
Pedersen(Australia sample)* (Pedersen et al., 2018)	2018	various (lung, colorectal)	Australia	healthy population	None	Adults aged 50 or over, recruited through random probability sampling.	4002	66	63	Low (11)	K, B
Pedersen (Canada sample)* (Pedersen et al., 2018)	2018	various (lung, colorectal)	Australia	healthy population	None	Adults aged 50 or over, recruited through random probability sampling.	2064	64	65	Low (11)	K, B
Pedersen (Denmark sample)* (Pedersen et al., 2018)	2018	various (lung, colorectal)	Australia	healthy population	None	Adults aged 50 or over, recruited through random probability	2000	64	53	Low (11)	K, B

						sampling.					
Pedersen (UK sample)* (Pedersen et al., 2018)	2018	various (lung, colorectal)	Australia	healthy population	None	Adults aged 50 or over, recruited through random probability sampling.	6965	65	46	Low (11)	K, B
Pedersen (Norway sample)* (Pedersen et al., 2018)	2018	various (lung, colorectal)	Australia	healthy population	None	Adults aged 50 or over, recruited through random probability sampling.	2009	64	61	Low (11)	K, B
Pedersen (Sweden sample)* (Pedersen et al., 2018)	2018	various (lung, colorectal)	Australia	healthy population	None	Adults aged 50 or over, recruited through random probability sampling.	2039	65	55	Low (11)	K, B
Akhtar* (Akther, Hossain, Al Kawsar, Hossain, & Das, 2018)	2018	breast	Bangladesh	patients	None	Newly diagnosed patients with primary carcinoma of the breast	200	42	100	Medium (8)	B
Moodley (Moodley, Cairncross, Naiker, & Constant, 2018)	2018	breast	South Africa	patients	None	Women diagnosed with breast cancer at a breast clinic.	187	54	100	Low (10)	K, I
Joffe (Joffe et al., 2018)	2018	breast	South Africa	patients	None	Female patients 18+ years old newly diagnosed with breast carcinoma.	499	63% are below 60	100	Medium (9)	K
Sayed* (Sayed et al., 2019)	2019	breast	Kenya	healthy population	None	Women aged 15-49 randomly selected from the primary healthcare database of the region.	402	22	100	Low (10)	K, B

Note: Average age is an approximation based on the available data in each study.

*Data obtained via personal correspondence with the original authors or calculated from data posted as supplementary material.

Supplementary material: Studies included in the meta-analysis

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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.	3-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6, 8
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.	7
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.	8
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.	7-9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Available on OSF and in the registration protocol: osf.io/95cvf/
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).	8

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.	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.	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.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
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.	11

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).	12, Suppl. materials
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12, Suppl. materials
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.	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.	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).	Table 1, more details in OSF: osf.io/95cvf/
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.	Figures 2-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2-6, p. 13-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13, Suppl. materials
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-17, Suppl. materials
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).	18-20
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).	18-20, 23-25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-22
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.	Title page

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(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary materials: SYMPTOMS KNOWLEDGE

MODERATOR AND SENSITIVITY ANALYSES

		Studies with healthy populations (k=19)							**Studies with patients (k=12)**							
	Moderator	**log OR**	**log 95% LL CI**	**log 95% UL CI**	**OR**	**95% LL CI**	**95% UL CI**	**I^2**	**log OR**	**log 95% LL CI**	**log 95% UL CI**	**OR**	**95% LL CI**	**95% UL CI**	**I^2**	**Study info.**
Moderator analyses	None (RE model)	**-.32**	**-.46**	**-.18**	**.73**	**.63**	**.84**	90	**-.92**	**-1.47**	**-.37**	**.40**	**.23**	**.69**	93	
	Delay definition	-.20	-.41	.00	.82	.66	1.00	89	**-.16**	**-.25**	**-.07**	**.85**	**.78**	**.93**	85	
	Risk of bias	-.13	-.28	.03	.88	.76	1.03	90	.13	-.45	.70	1.14	.64	2.01	94	
	Adjusted vs. unadjusted effect	-.05	-.35	.24	.95	.70	1.27	91	-.18	-1.49	1.12	.84	.23	3.06	93	
	Gender composition (mixed vs female)	**-.42**	**-.66**	**-.19**	**.66**	**.52**	**.83**	83	.43	-.71	1.57	1.54	.49	4.81	93	

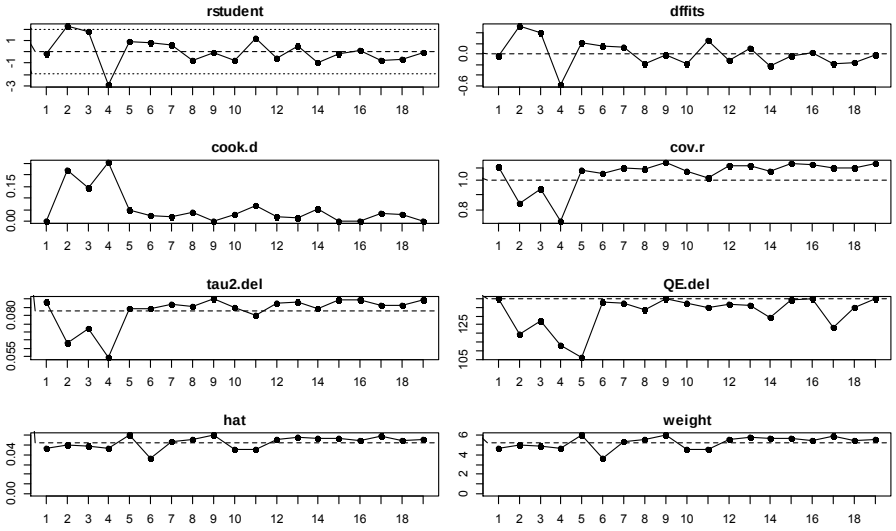
	Use of theoretical model (yes vs no)	.27	-.02	.57	1.31	.98	1.77	90	.59	-.81	2.00	1.80	.44	7.39	93	
Sensitivity analyses	Effect size transformed vs not	.16	-.12	.44	1.17	.89	1.55	91	.88	-1.02	2.78	2.41	.36	16.12	94	
	Without studies at high risk of bias	-	-	-	-	-	-	-	**-.85**	**-1.41**	**-.30**	**.43**	**.24**	**.74**	94	Harirchi et al.
	Without studies that are outliers	-	-	-	-	-	-	-	**-.48**	**-.69**	**-.27**	**.62**	**.50**	**.76**	42	Ouasmani et al.

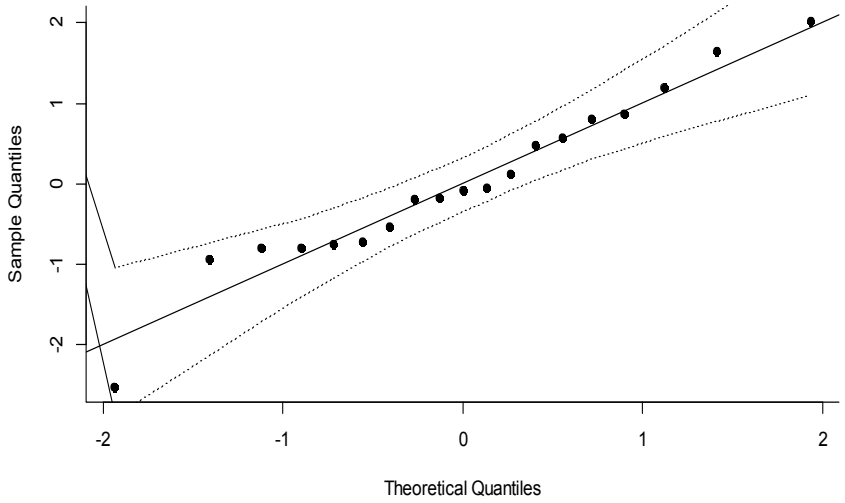
OUTLIER ANALYSES

Symptoms knowledge: Studies with healthy populations (k=19)

Influence plots and Normal Q-Q plot. Studies that diverge from the common model (if present) are conveniently marked in red.

Reference: Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 2010;36(3).



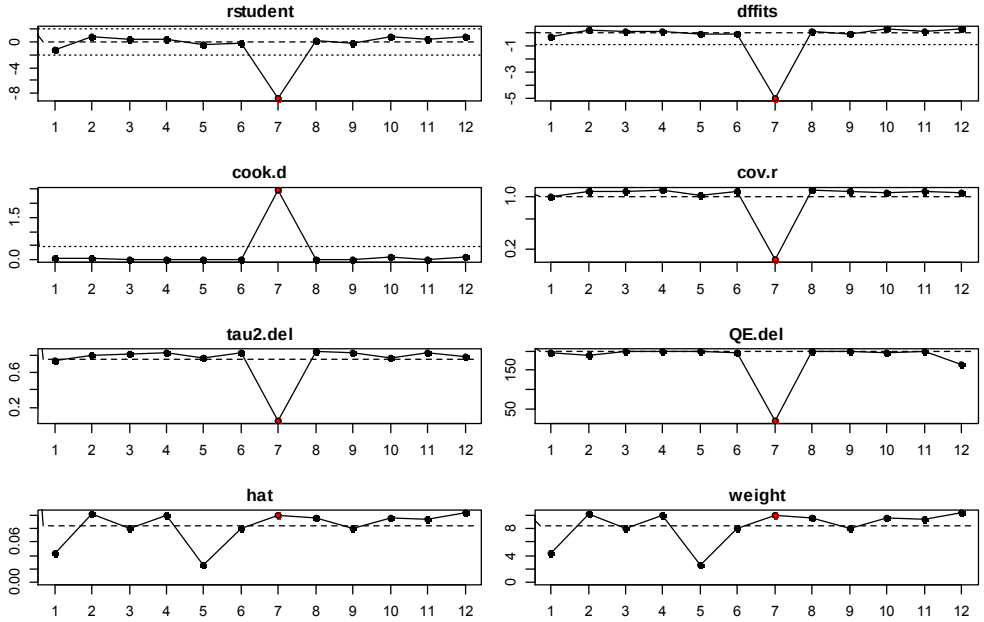


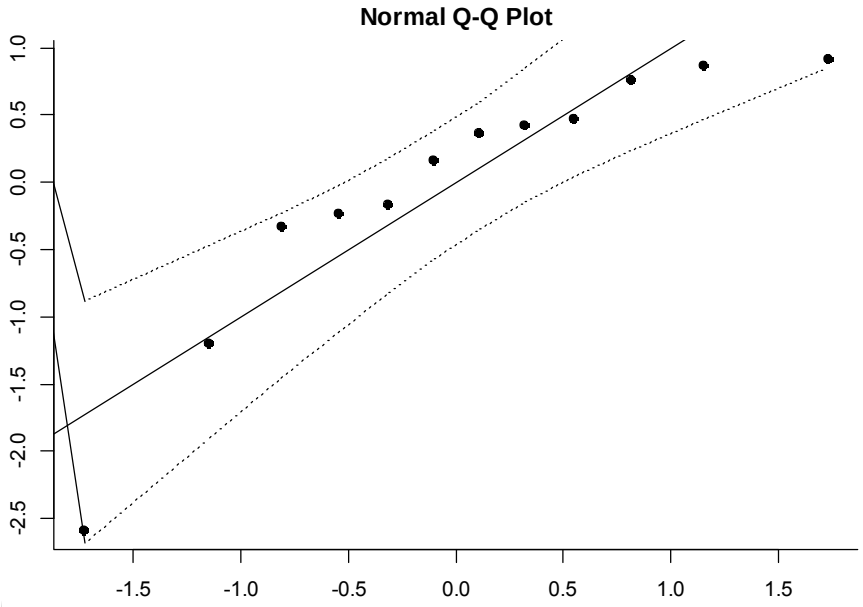
OUTLIER ANALYSES

Symptoms knowledge: Studies with patients (k=12)

Influence plots and Normal Q-Q plot. Studies that diverge from the common model (if present) are conveniently marked in red.

Reference: Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 2010;36(3).





PUBLICATION BIAS ANALYSES

Symptoms knowledge: Studies with healthy populations (k=19)

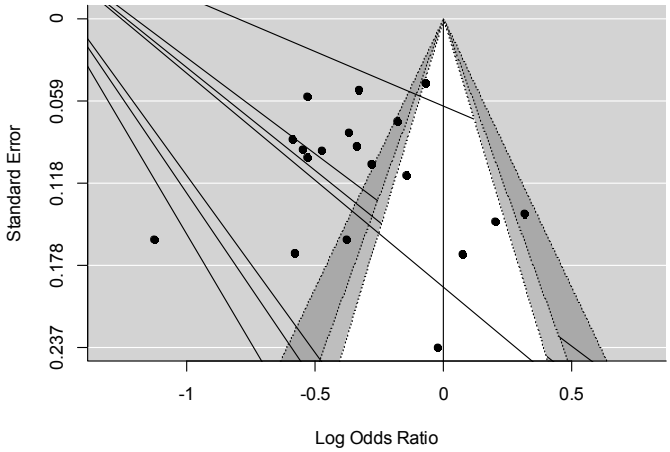
Test for funnel plot asymmetry: z = 0.62, p = 0.54

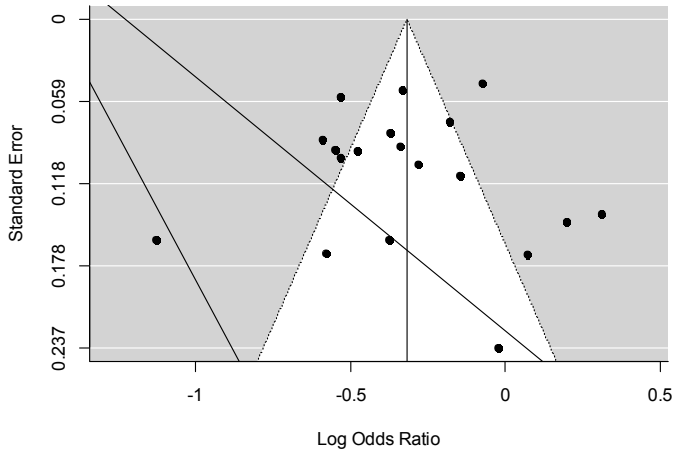
On the left: A contour-enhanced funnel plot. The unshaded (i.e., white) region in the middle corresponds to P-value >.10, the gray-shaded region to P-values between .10 and .05, the dark

gray-shaded region to P-values between .05 and .01, and the region outside of the funnel corresponds to P-values <.01. If studies appear to be missing in areas of statistical nonsignificance (i.e., white areas), publication bias is likely

On the right: A regular funnel plot.

Reference: Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008 Oct;61(10):991-996.





PUBLICATION BIAS ANALYSES

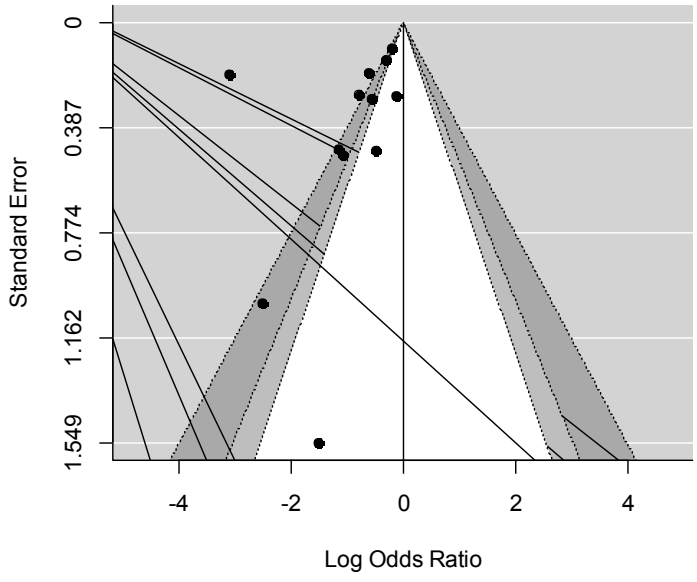
Symptoms knowledge: Studies with patients (k=12)

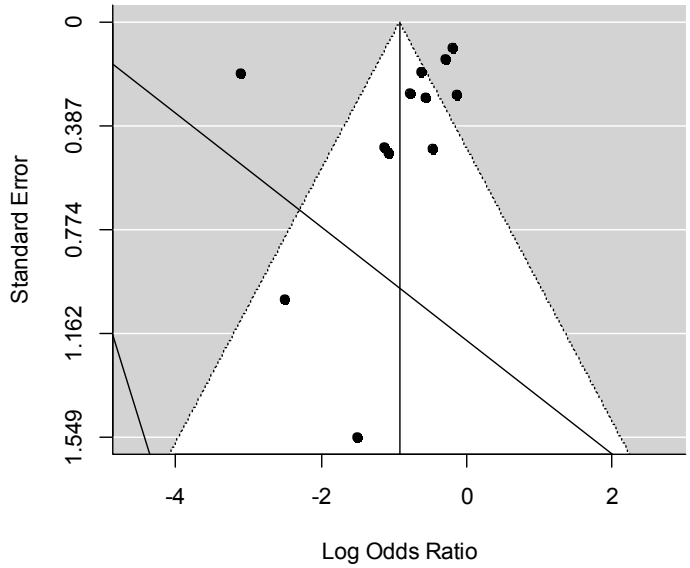
Test for funnel plot asymmetry: z = -0.98, p = 0.33

On the left: A contour-enhanced funnel plot. The unshaded (i.e., white) region in the middle corresponds to P-value >.10, the gray-shaded region to P-values between .10 and .05, the dark gray-shaded region to P-values between .05 and .01, and the region outside of the funnel corresponds to P-values <.01. If studies appear to be missing in areas of statistical nonsignificance (i.e., white areas), publication bias is likely

On the right: A regular funnel plot.

Reference: Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidem





ECOLOGICAL ANALYSES (COUNTRY INDICATORS)

1. GINI (grouped: fairly unequal vs. fairly equal)

Symptoms knowledge, k=31	**logOR**	**log 95% LLCI**	**log 95% ULCI**	**OR**	**95% LLCI**	**95% ULCI**	**I^2**
Simple meta-regression model							96
GINI group*	**-.50**	**-.93**	**-.08**	**.60**	**.39**	**.92**	
Multiple meta-regression model							89
GINI group	-.28	-.58	.03	.76	.56	1.03	
Type (patient vs. healthy pop.)	.22	-.17	.60	1.25	.84	1.82	
Delay definition	-.19	-.25	-.13	.83	.78	.88	

*GINI group ORs are for “fairly unequal” (>35) vs. “fairly equal” (≤35).

1. GINI (continuous score)

Symptoms knowledge, k=29	**logOR**	**log 95% LLCI**	**log 95% ULCI**	**OR**	**95% LLCI**	**95% ULCI**	**I^2**
Simple meta-regression model							97
GINI coefficient*	**-.06**	**-.11**	**-.003**	**.94**	**.90**	**.99**	
Multiple meta-regression model							89
GINI coefficient	-.03	-.07	.00	.97	.94	1.00	
Type (patient vs. healthy	.16	-.30	.61	1.17	.74	1.84	

pop.)							
Delay definition	-.19	-.26	-.12	.83	.77	.89	

*Original coefficient (score 0 to 100); Without outlier South Africa (country with the highest income inequality in the world, GINI=63)

Supplementary materials: SYMPTOM INTERPRETATION

(attribution to cancer vs. other)

MODERATOR AND SENSITIVITY ANALYSES

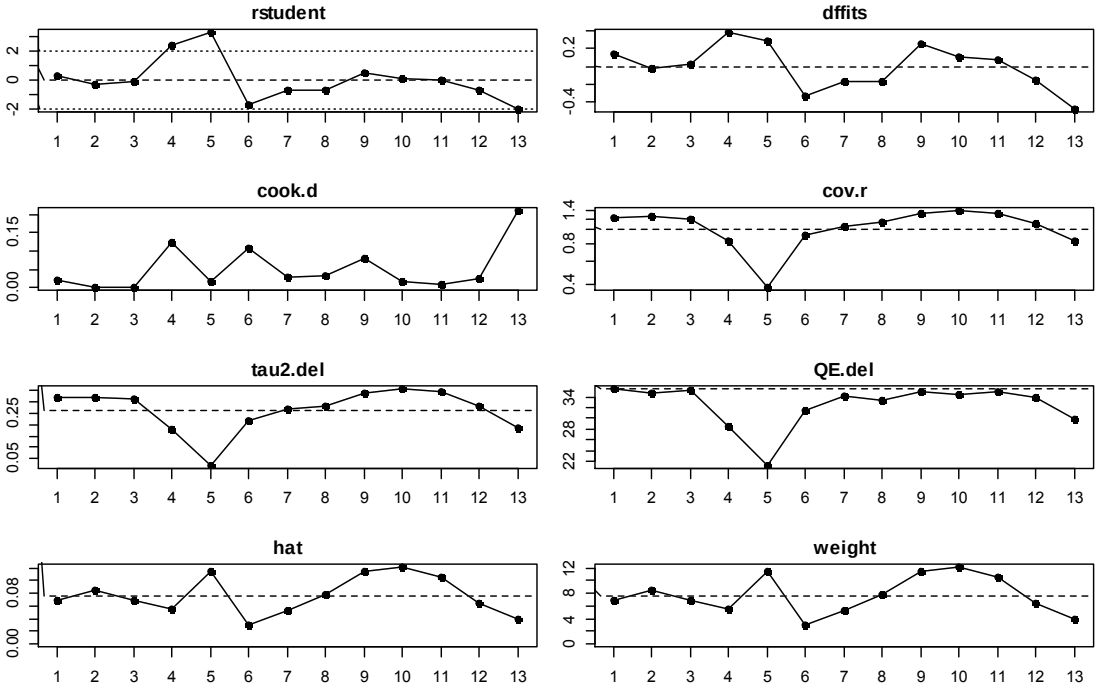
		Studies with patients (k=13)							
	Moderator	**logOR**	**log 95% LLCI**	**log 95% ULCI**	**OR**	**95% LLCI**	**95% ULCI**	**I^2**	**Study info.**
Moderator analyses	None (RE model)	**-.66**	**-1.03**	**-.29**	**0.52**	**0.36**	**0.75**	69	
	Delay definition	-.03	-.10	.04	0.97	0.90	1.04	67	
	Risk of bias	.08	-.22	.37	1.08	0.80	1.45	72	
	Adjusted vs. unadjusted effect	-.20	-1.01	.60	0.82	0.36	1.82	67	
	Gender composition (mixed vs female)	.51	-.17	1.19	1.67	0.84	3.29	59	
	Use of theoretical model (yes vs no)	.38	-.57	1.32	1.46	0.57	3.74	69	
Sensitivity analyses	Effect size transformed vs not	.09	-.71	.90	1.09	0.49	2.46	72	
	Without studies at high risk of bias	**-.54**	**-.88**	**-.19**	**0.58**	**0.41**	**0.83**	64	Panzarella et al.; Andersen et al.
	Without studies that are outliers	-	-	-	-	-	-	-	-

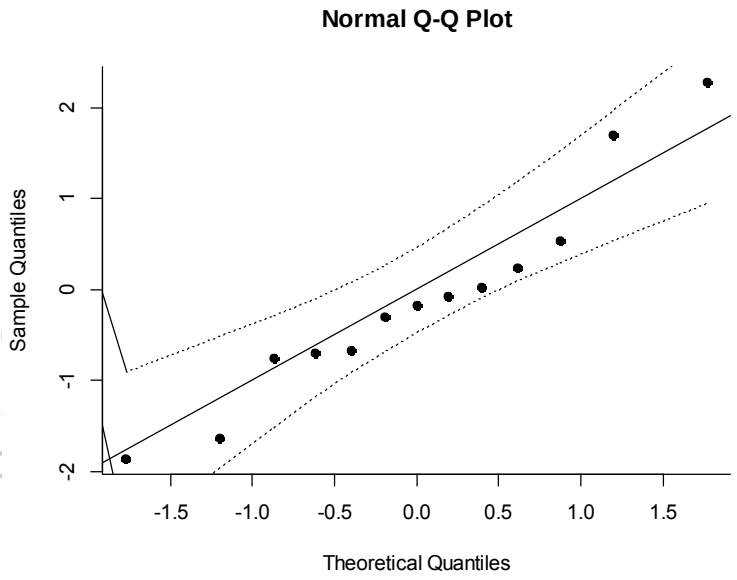
OUTLIER ANALYSES

Symptoms interpretation: Studies with patients (k=13)

Influence plots and Normal Q-Q plot. Studies that diverge from the common model (if present) are conveniently marked in red.

Reference: Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 2010;36(3).





PUBLICATION BIAS ANALYSES

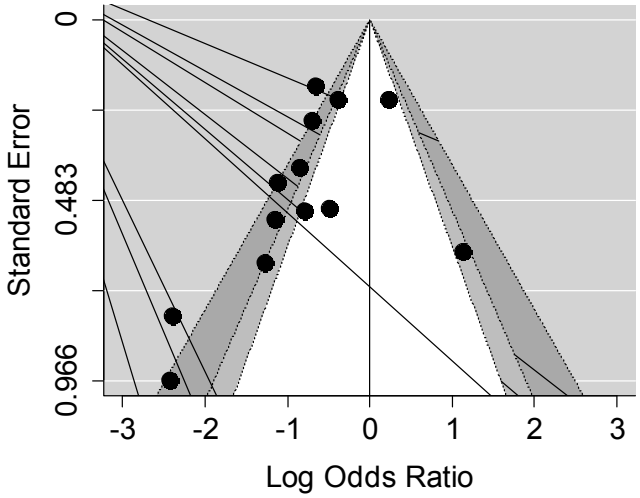
Symptoms interpretation: Studies with patients (k=13)

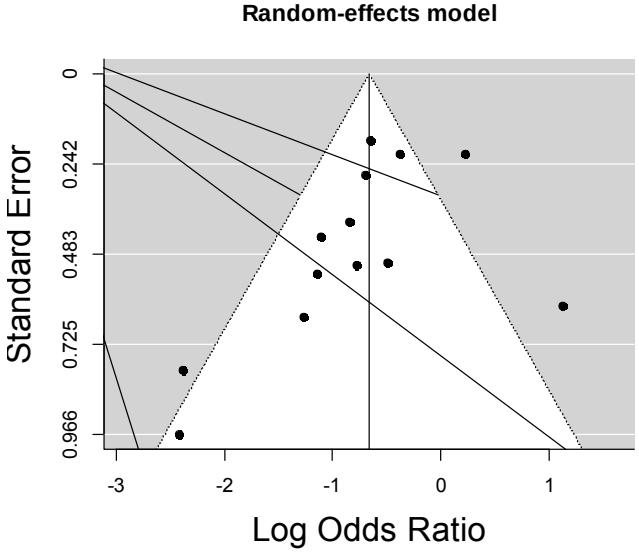
Test for funnel plot asymmetry: z = -2.05, p = 0.04. This test is significant at p<.05; however, the asymmetry is not consistent with a publication bias. Instead, larger studies seem to report smaller effects.

On the left: A contour-enhanced funnel plot. The unshaded (i.e., white) region in the middle corresponds to P-value >.10, the gray-shaded region to P-values between .10 and .05, the dark gray-shaded region to P-values between .05 and .01, and the region outside of the funnel corresponds to P-values <.01. If studies appear to be missing in areas of statistical nonsignificance (i.e., white areas), publication bias is likely

On the right: A regular funnel plot.

Reference: Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008 Oct;61(10):991-996.





ECOLOGICAL ANALYSES (COUNTRY INDICATORS)

1. GINI (grouped: fairly unequal vs. fairly equal)

Symptom interpretation, k=13	**logOR**	**log 95% LLCI**	**log 95% ULCI**	**OR**	**95% LLCI**	**95% ULCI**	**I^2**
Simple meta-regression model							39
GINI group*	**-.67**	**-1.22**	**-.12**	**.51**	**.30**	**.89**	

*GINI group ORs are for "fairly unequal" (>35) vs. "fairly equal" (≤35).

1. GINI (continuous score)

Symptoms interpretation, k=12	**logOR**	**log 95% LLCI**	**log 95% ULCI**	**OR**	**95% LLCI**	**95% ULCI**	**I^2**
Simple meta-regression model							65
GINI coefficient*	-.04	-.12	.04	.96	.89	1.04	

*Original coefficient (score 0 to 100); Without outlier South Africa (country with the highest income inequality in the world, GINI=63)

Supplementary materials: BELIEFS ABOUT CANCER

MODERATOR AND SENSITIVITY ANALYSES

		Studies with healthy populations (k=11)							**Studies with patients (k=7)**							
	Moder	**log**	**log**	**log**	**O**	**95%**	**95%**	**I^2**	**log**	**log**	**log**	**O**	**95%**	**95%**	**I^2**	**Study**

	ator	OR	95 % LL CI	95 % UL CI	R	LL CI	UL CI		OR	95 % LL CI	95 % UL CI	R	LL CI	UL CI		info .
Moderator analyses	None (RE model)	**-.36**	**-.65**	**-.08**	**.70**	**.52**	**.92**	84	**-.67**	**-1.14**	**-.20**	**.51**	**.32**	**.82**	83	
	Delay definition	-.19	-.58	.21	.83	.56	1.23	83	-.03	-.11	.04	.97	.90	1.04	85	
	Risk of bias	**-.37**	**-.65**	**-.09**	**.69**	**.52**	**.91**	72	.01	-.25	.28	1.01	.78	1.32	87	
	Adjusted vs. unadjusted effect	**-.62**	**-1.12**	**-.11**	**.54**	**.33**	**.90**	74	-.43	-1.37	.52	.65	.25	1.68	80	
	Gender composition (mixed vs female)	-.36	-.93	.2	.70	.39	1.22	82	**-.95**	**-1.59**	**-.32**	**.39**	**.20**	**.73**	56	
	Use of theoretical model (yes vs no)	**.73**	**.32**	**1.13**	**2.08**	**1.38**	**3.10**	61	.03	-1.42	1.47	1.03	.24	4.35	85	
Sensitivity analyses	Scale (fatalism vs other)	-	-	-	-	-	-	-	.08	-1.03	1.19	1.08	.36	3.29	81	
	Effect size transformed vs not	**.73**	**.39**	**1.07**	**2.07**	**1.47**	**2.92**	51	.43	-.66	1.52	1.54	.52	4.57	83	
	Without studies at high risk of bias	-	-	-	-	-	-	-	**-.71**	**-1.25**	**-.16**	**.49**	**.29**	**.85**	**86**	Harirchi et al.

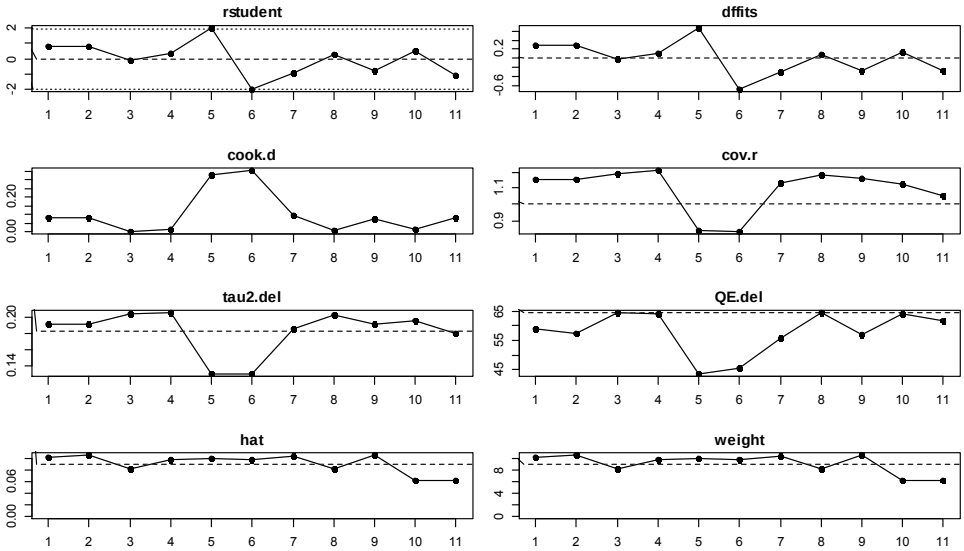
	Without studies that are outliers	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

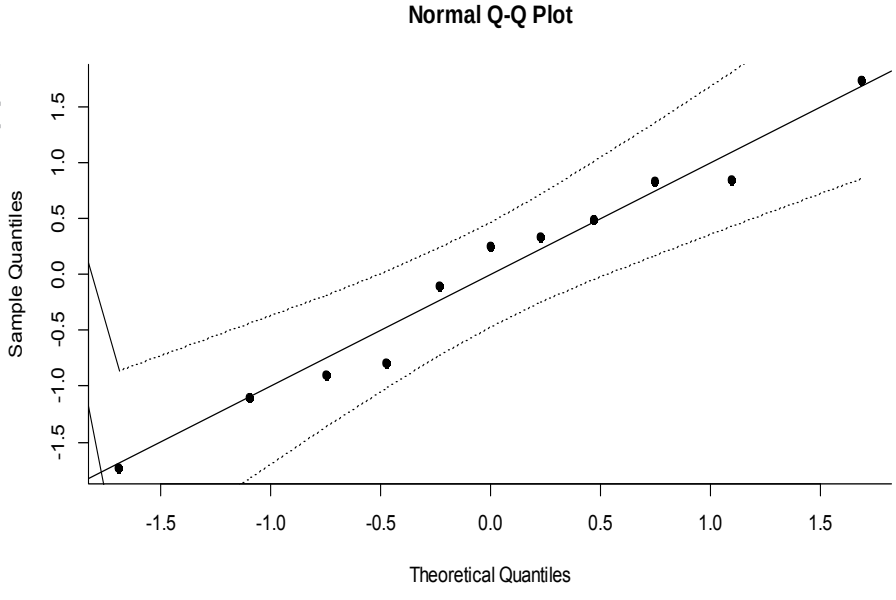
OUTLIER ANALYSES

Beliefs about cancer: Studies with healthy populations (k=11)

Influence plots and Normal Q-Q plot. Studies that diverge from the common model (if present) are conveniently marked in red.

Reference: Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 2010;36(3).



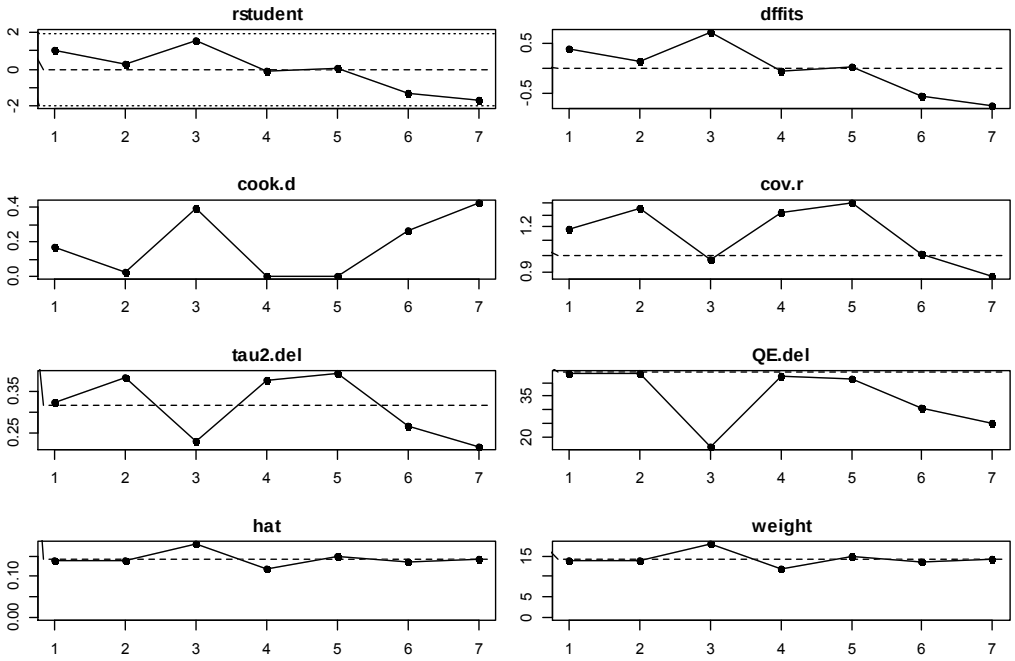


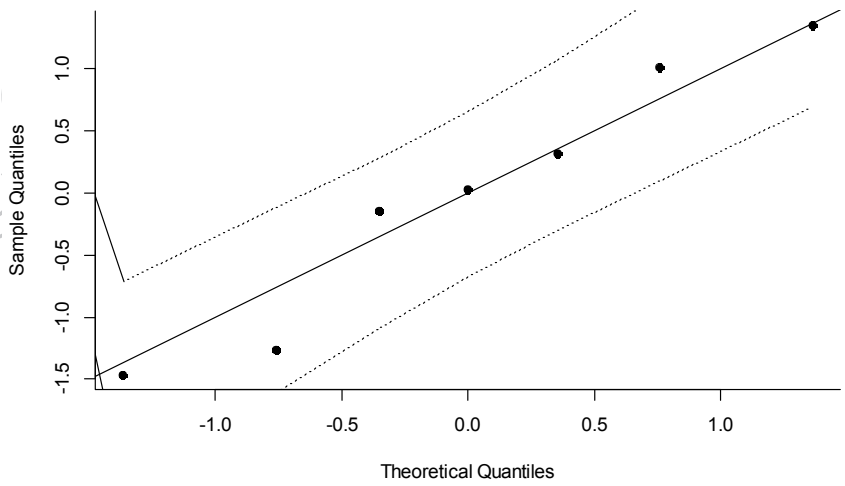
OUTLIER ANALYSES

Beliefs about cancer: Studies with patients (k=7)

Influence plots and Normal Q-Q plot. Studies that diverge from the common model (if present) are conveniently marked in red.

Reference: Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 2010;36(3).

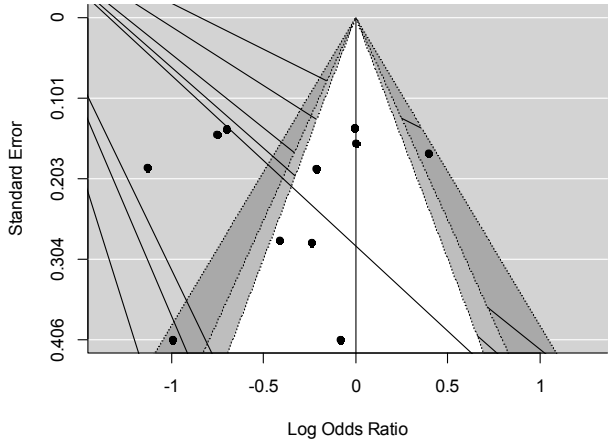


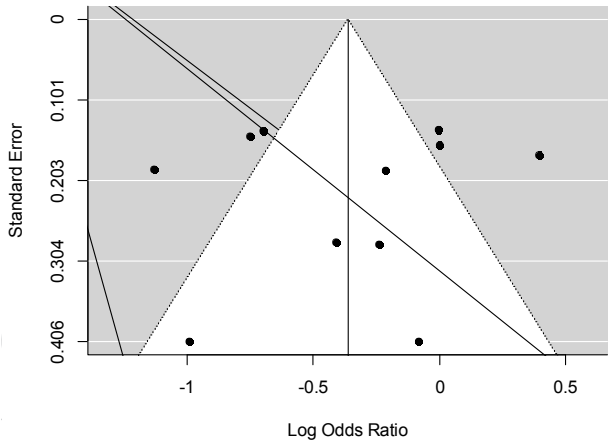


On the left: A contour-enhanced funnel plot. The unshaded (i.e., white) region in the middle corresponds to P-value >.10, the gray-shaded region to P-values between .10 and .05, the dark gray-shaded region to P-values between .05 and .01, and the region outside of the funnel corresponds to P-values <.01. If studies appear to be missing in areas of statistical nonsignificance (i.e., white areas), publication bias is likely

On the right: A regular funnel plot.

Reference: Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008 Oct;61(10):991-996.





PUBLICATION BIAS ANALYSES

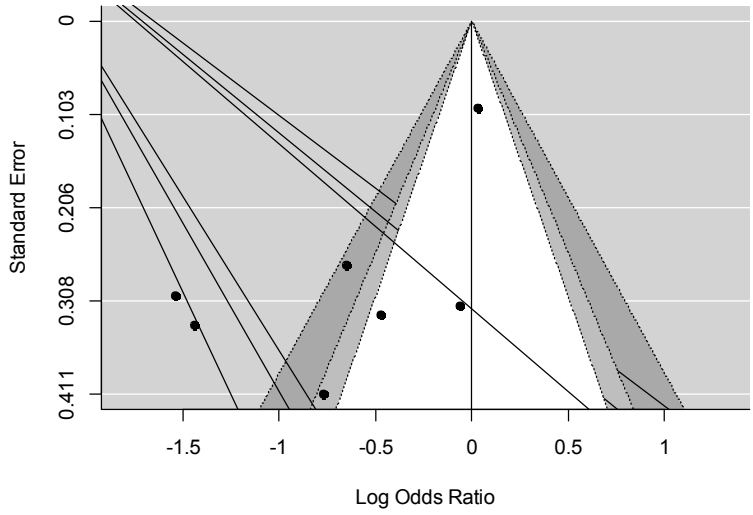
Beliefs about cancer: Studies with patients (k=7)

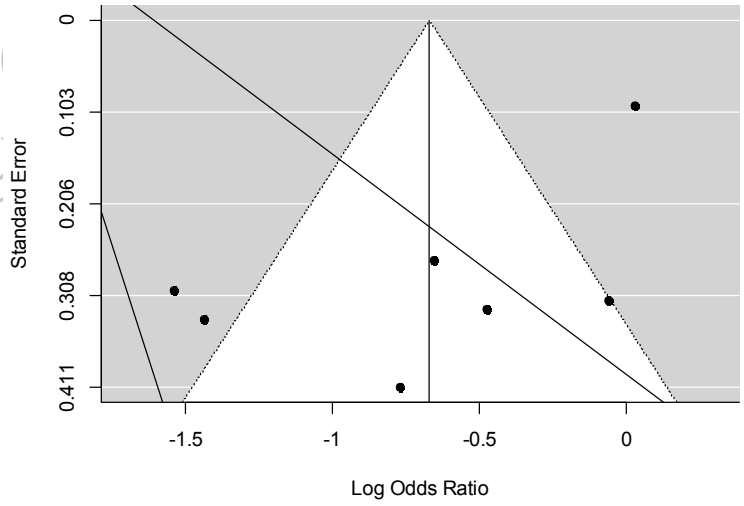
Test for funnel plot asymmetry: z = -1.43, p = 0.15

On the left: A contour-enhanced funnel plot. The unshaded (i.e., white) region in the middle corresponds to P-value >.10, the gray-shaded region to P-values between .10 and .05, the dark gray-shaded region to P-values between .05 and .01, and the region outside of the funnel corresponds to P-values <.01. If studies appear to be missing in areas of statistical nonsignificance (i.e., white areas), publication bias is likely

On the right: A regular funnel plot.

Reference: Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008 Oct;61(10):991-996.





Additional information

- Author contributions. DP conceived the research, collected, analyzed, and interpreted the data, and wrote the first draft of the manuscript. YO collected, analyzed, and interpreted the data, and revised the manuscript for critical content. ESF and SDL collected and interpreted the data, and revised the manuscript for critical content. MJS conceived the research, interpreted the data and revised the manuscript for critical content. MRB revised the analysis and interpreted the data and revised the manuscript for critical content. All authors approved the final version of the manuscript.
- Ethical approval: This was analysis of secondary data and no ethical approval was required for data collection.
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