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Depression and Anxiety in Prostate Cancer: A Systematic Review and Meta-Analysis of Prevalence Rates

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Abstract

Objectives: To systematically review the literature pertaining to the prevalence of depression and anxiety in prostate cancer patients as a function of treatment stage.

Design: Systematic review and meta-analysis

Participants: 4494 prostate cancer patients from primary research investigations.

Primary Outcome Measure: The prevalence of clinical depression and anxiety in prostate cancer patients as a function of treatment statge

Results: We identified 27 full journal articles that met the inclusion criteria for entry into the meta-analysis resulting in a pooled sample size of 4494 patients. The meta-analysis of prevalence rates identified pre-treatment, on-treatment and post-treatment depression prevalences of 17.27% (95% CI: 15.06%-19.72%), 14.70% (95% CI: 11.92%-17.99%) and 18.44% (95% CI: 15.18%-22.22%) respectively. Pre-treatment, on-treatment and post-treatment anxiety prevalences were 27.04% (95% CI: 24.26%-30.01%), 15.09% (95% CI: 12.15%-18.60%) and 18.49% (95% CI: 13.81%-24.31%) respectively.

Conclusions: Our findings suggest that the prevalence of depression and anxiety in men with prostate cancer, across the treatment spectrum, are relatively high and in keeping with that observed in other cancer sites. In light of the growing emphasis placed on cancer survivorship we consider that further research within this area is warranted to ensure psychological distress in prostate cancer patients is not under-diagnosed and under-treated.

Article Summary

Article Focus:

- Identifying systematically how the prevalence of anxiety and depression in men with prostate cancer varies across the treatment trajectory, from pre-treatment to post-treatment follow up

Key Messages:

- Prostate cancer patients display a significantly higher prevalence of depression and anxiety than the normal population across the treatment spectrum, particularly prior to and after the completion of treatment.
- This has important implications for decision making, quality of life and survivorship in this population.
- Further research is required to ensure that psychological distress in men with prostate cancer is clearly identified and managed appropriately

Strengths and Limitations:

- This is the first meta-analysis to define depression and anxiety prevalence specifically within prostate cancer
- Limited data is available for patients on active surveillance and with metastatic disease.
- Cross-sectional methodologies make it difficult to draw definitive conclusions about the history and progression of anxiety and depression over the cancer journey in this population.

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Competing Interests: None declared.

Introduction

Prostate cancer (PCa) represents the most common form of non-cutaneous malignancy diagnosed in British men (1). Over 36,000 new cases were diagnosed in 2007, accounting for almost 25% of the total yearly number of male cancer diagnoses (1). With an ageing UK population and increasing utilisation of PCa screening in asymptomatic men (2) the incidence rates of PCa are predicted to continue increasing year on year (1).

In light of such a substantial and sustained disease burden the management of survivorship issues within PCa becomes of paramount importance. Such issues revolve around the effective maintenance of quality of life (QoL) throughout the cancer journey, from initial diagnosis through to post-treatment survivorship. In addition to generic QoL issues, current National Cancer Survivorship Initiative (NCSI) guidelines have identified the need for better assessment, diagnosis and treatment of the specific psychological conditions associated with cancer diagnoses and treatment as one of the five key goals of improved, personalised and patient centred cancer care within the UK (3).

Depression and anxiety are two of the most commonly experienced psychological conditions experienced by cancer patients (4) and are associated with unique psycho-physiological side effects that importantly encompass poorer treatment outcomes (6), increased periods of hospitalisation (5) and higher mortality rates (7). With the advances in treatment efficacy, cancer is being increasingly viewed and treated as a chronic disease that can be effectively managed for many years. Given the longevity associated with the trajectory of PCa (over 70% of PCa patients can expect to live for ten years or more from the time of diagnosis) it is possible that the onset of psychological distress within this population of men is not an acute threat that quickly passes but a chronic one with peaks and troughs of severity that occur at key stages of the cancer journey.

The research base evaluating the prevalence of depression and anxiety within PCa is growing steadily and a sizeable body of clinically relevant research currently exists. Unfortunately much of this data is very heterogeneous and of poor methodological quality and has yet to be subjected to rigorous systematic review and meta-analysis. This lack of synthesis makes it very difficult for physicians and allied health care professionals working with PCa to access, interpret and apply the key research findings to their clinical practice.

It is as yet unclear what stages of the PCa cancer journey patients find most distressing. Were this known, or at least better understood, it would allow health care professionals to be more proactive and aware of what stages of treatment patients are most likely to experience

depression and anxiety which would allow the health care team to "risk-adapt" their psychological screening and support processes.

The current meta-analysis was undertaken to address this issue and provide an initial baseline estimate of the incidence of clinical depression and anxiety in PCa patients during each of the three key stages of cancer treatment; pre-treatment, on-treatment and post-treatment.

Method

Eligibility Criteria

Studies that investigated the specific prevalence of depression and anxiety in prostate cancer (PCa) patients in full journal articles were included. Studies published in conference proceedings, qualitative research, commentaries and discussions, letters, books, book chapters or research not published in the English language were excluded.

Eligible studies were restricted to research focusing on individuals with a biopsy confirmed diagnosis of PCa. If PCa patients were included within an investigation that recruited mixed cancer populations, the study was required to have reported data about the PCa patients as a distinct sub-sample. The primary outcome for the current meta-analysis was the prevalence of depression and anxiety. Thus inclusion into the meta-analysis was restricted to those studies that reported PCa specific prevalence data for depression and anxiety separately.

To be eligible for inclusion, each study was required to provide a clear definition of the PCa treatments undertaken by the study participants and when such treatments took place (i.e. treatment that was yet to be undertaken, was being undertaken at the time of the study or had already been completed. For the latter category, it was a requirement that the authors specified the time lapse since the cessation of treatment).

Questionnaire Analysis

Entry into the meta-analysis was also restricted to data that was collected from questionnaires that provided specific, valid and reliable measurements of depression and anxiety. To enable this, a series of questionnaire specific inclusion criteria were created against which all of the questionnaires utilised in the studies could be assessed; each questionnaire must:

1. Allow for the specific and independent measurement of depression and anxiety.

2. Have available established threshold information (measurements) for the diagnosis of depression and anxiety.

3. The validity of each questionnaire must have been assessed in comparison to established “gold standard” questionnaires.

4. The internal validity and reliability of each questionnaire must have been assessed and deemed acceptable (test-retest).

Twelve questionnaires meeting the criteria were identified which included the Hospital Anxiety and Depression Scale, Stait -Trait Anxiety Scale, Centre for Epidemiologic Studies Depression Scale, Symptom Checklist, Beck Depression Inventory, Self-Rating Anxiety Scale, Self-Rating Depression Scale, Brief Symptom Inventory, Composite International Diagnostic Interview, Memorial Anxiety Scale for Prostate Cancer and the Effects of Prostate Cancer on Lifestyle Questionnaire

Identifying Research Evidence

We searched 6 electronic databases (OVID Medline, EMBASE, AMED, PsycINFO, CINAHL and Web of Science) for articles that met the previously discussed criteria using pre-specified MESH terms as that included Prostate Neoplasm (EXP)” OR “Prostate Cancer” AND “Depression (EXP)” or “Anxiety (EXP)” or “Psychological distress (EXP” or “Stress (EXP)” or “Distress (EXP)”.

To supplement the electronic searches we also conducted searches of the reference lists of previous reviews, key papers and other relevant articles identified by the electronic search. We also conducted systematic searches of the content lists of key journals to identify any additional studies missed by the electronic search.

Study Selection

Titles and abstracts were initially assessed for eligibility. If it was possible to confirm that an article met the inclusion criteria from the abstract alone, the full text article was retrieved. If it was clear from the abstract that an article was not eligible, it was rejected immediately. If it was not possible to determine the eligibility of an article from the abstract, the full text article was retrieved. If any key information was missing, we contacted the authors for the missing data. If this was not possible or ineffective, the study was rejected, (see Figure 1).

Data Extraction

The following specific information relating to data collection and results was extracted individually from each identified article and entered into a pre-designed Excel spread sheet: date and geographical location of data collection; aims and objectives of the investigation; study design; participant inclusion and exclusion criteria; recruitment procedures; sample size; disease stage; socio-demographic status (age, ethnicity and relationship, educational and employment status); time since diagnosis; additional co-morbidity; stage of treatment (pre, on or post-treatment); treatments undertaken (surgery, radiotherapy, hormone therapy, chemotherapy, active-surveillance/watchful waiting); questionnaires utilised; statistical analyses performed; depression prevalence (%) and anxiety prevalence (%).

To test the consistency of data extraction across the studies, three researchers (SW, LL, SE) extracted data from the same 6 articles then compared the results of their extraction. A points system was utilised to allow for the objective assessment of consistency. 1 point was allocated for variables with identical data extraction and 0 points for variables with differences. Across all ratings, consistency ranged from 92% to 96% (median: 94%).

Meta-Analysis Procedure

Given the range of estimated proportions expected within the extracted data, the logits of proportions method of conducting the statistical analysis was employed, rather than utilising normal approximations of binomial distributions.

Cochran's Q test was applied to the logits to test the hypothesis of homogeneity of the within study estimates of the proportions, with larger Q values suggesting that the estimates are not homogeneous. Initial analyses highlighted Q values between Q= 15.2 and 215, with some of the larger values suggesting a degree of heterogeneity, the result in some cases of only one or two studies being out of line with the others. For completeness, meta-analysis results have been provided even for those cases where heterogeneity is evident.

Results

Search Results

The electronic database searches initially yielded 1778 journal article references. 1655 of these were subsequently removed due to either duplication or a failure to meet the inclusion criteria. Full text articles were then retrieved and critically appraised for the remaining 123 journal references. Of these 123 articles 97 did not meeting the inclusion criteria. The remaining 26 articles were entered into the meta-analysis.

Hand searches of the key journals identified by the electronic database search revealed no additional journal articles. Searching the reference lists of articles identified through the electronic database search identified 2 journal article references of interest that had otherwise been missed. Full text articles were retrieved for these 2 references, one of which could be included making the total included 27. (Figure 1).

INSERT FIGURE 1

Study Locations

Of the 27 studies entered into the review, 9 were conducted within America (5,8,9,10,12,13,14,15,16), 4 in both Australia (17,18,19,20) and Holland (21,22,23,24), 3 in the UK (25,26,27), 2 each in Sweden (28,29), Germany (30,31) and Canada (32,33) and 1 in Finland (34).

Study Sample Sizes

The samples sizes of the studies entered into the review varied widely from 36 to 861. The total sample size across all 27 studies was 4494 with a mean sample size of 158. The sample sizes of the individual treatment stage groups (pre, on and post-treatment) can be seen in Table 1.

Participant Age

Data on participant age was reported by 24 of the 27 studies and in all 24 cases mean age was reported. The range of mean ages across the 24 studies varied from 57.5 years to 73.2 years. The mean age of all participants across the 24 studies was 66.3 years (3.3). Three studies failed to report participant age in any format. The mean age of the participants in each of the three treatment groups can be seen in Table 1.

Cancer Staging

Data regarding participant cancer stage was reported by 23 of the 27 studies. There was a general lack of consistency regarding reporting methods. Several studies utilised the clinical T-staging system of T1 (localised) to T4 (metastatic) whilst the majority simply graded PCa as localised, advanced or metastatic. No study reported patient disease stage using the

recommended tumour-nodes-metastasis (TNM). The majority of patients had been diagnosed with localised disease (n=3270), followed by advanced (513) and metastatic PCa (87), as shown in Table 1.

INSERT TABLE 1

Cancer Treatments Undertaken

Table 2 provides an overview of the number of participants undergoing each PCa treatment. Unfortunately, it was not possible to stratify the treatments undertaken as a function of either disease stage (localised, advanced or metastatic) or treatment stage (on-treatment or post-treatment). Thus the data in Table 2 provides a collective overview of the treatments undertaken by all of the patients, irrespective of disease or treatment stage. Additionally, several of the "pre-treatment" studies recruited participants who had yet to decide upon treatment. Such patients are listed in Table 4 as 'newly diagnosed'.

INSERT TABLE 2

2.6. Questionnaires Analysis

Of the 12 questionnaires meeting the questionnaire inclusion criteria as listed in the method section, only 7 were utilised by the 27 studies entered into this meta-analysis. Table 5 lists the 7 questionnaires and the frequency with which they were used.

INSERT TABLE 3

Meta-Analysis of Depression and Anxiety Prevalence

Number of studies reporting depression

26 of the 27 studies entered into the review reported data on depression prevalence. Of these 26, 13 reported depression in pre-treatment patients, 9 in on-treatment patients, and 13 in post-treatment patients. The number of total studies from the 3 groups exceeded 27 as several longitudinal studies reported depression in multiple treatment groups (i.e. in both pre-treatment and on-treatment groups).

Number of studies reporting anxiety

20 of the 26 studies entered into the review reported data on anxiety prevalence. Of these 20, 9 reported depression in pre-treatment patients, 4 in on-treatment patients and 11 in post-treatment patients.

Number of Patients Measured for Depression

Collectively, measures of depression were recorded from 5139 participants across the 26 studies. In terms of the individual treatment groups, 1259 participants provided measures of depression in the pre-treatment group, 723 in the on-treatment group and 3157 in the post treatment group.

Number of Patients Measured for Anxiety

Collectively, measures of anxiety were recorded from 4635 participants across the 20 studies. In terms of the individual treatment groups, 1057 participants provided measures of anxiety in the pre-treatment group, 501 in the on-treatment group and 3077 in the post treatment group.

Pre-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of depression was 17.27% (CI: 15.06%-19.72%).

Anxiety: Within the 9 studies that provided measures of anxiety in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of anxiety was 27.04% (CI: 24.26%-30.01%).

INSERT FIGURE 2

On-Treatment Depression and Anxiety Prevalence

Depression: Within the 9 studies that provided measures of depression in PCa patients currently undergoing treatment (see Figure 2), the prevalence of depression was 14.70% (CI: 11.92%-17.99%).

Anxiety: Within the 4 studies that provided measures of anxiety in PCa patients currently undergoing treatment (see Figure 2), the prevalence of anxiety was 15.09% (CI: 12.15%-18.60%).

INSERT FIGURE 3

Post-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients who had completed treatment (see Figure 3), the prevalence of depression was 18.44% (CI: 15.18%-22.22%).

Anxiety: Within the 11 studies that provided measures of anxiety in PCa patients who had completed treatment (see Figure 3), the prevalence of anxiety was 18.49% (CI: 13.81%-24.31%).

INSERT FIGURE 4

Depression and Anxiety Prevalence Across and Within Treatment Groups

Figure 4 provides a pictorial representation of the prevalence of depression and anxiety both within and across each of the three treatment groups.

INSERT FIGURE 5

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Discussion

There is a real need within clinical oncology, particularly as the burden of disease is escalating with improved diagnosis and treatment, for an increased awareness about the issue of psychological distress among men diagnosed with, being treated for and surviving through/living with a PCa diagnosis. The results of the current meta-analysis go some way in addressing this issue by providing those working within the field of PCa with a rigorous overview of the likely prevalence of depression and anxiety in the patients they treat. Our findings suggest that over the trajectory of the PCa journey, depression and anxiety prevalence are highest in patients who have yet to undergo treatment (17.27% and 27.4% respectively), lowest in patients who are currently undertaking treatment (14.70% and 15.90% respectively) before rising again in patients who have completed treatment (18.44% and 18.49% respectively). The relatively small variation observed within these prevalence rates across the different treatment stages, along with the large collective sample size of the meta-analysis (4494) suggests these conclusions are valid powerful and robust summaries of the data available. The prevalence of clinical depression in British men aged 65 years is estimated to be less than 9% (37order of refs right?). Such data are in stark contrast to the prevalence reported in PCa patients of the same age in this study.

The current meta-analysis is the first of its kind to specifically assess the prevalence of clinical depression and anxiety in prostate cancer (PCa) patients over their treatment spectrum, from pre-treatment, through treatment to post-treatment follow up. To date, the lack of synthesis of the available data relating to depression and anxiety in PCa has meant that clinical decisions have been based on isolated research trials that lack sufficient power and depth in terms of sample sizes, treatment protocols and treatment stages. Consequently the true prevalence of psychological morbidity experienced by PCa patients across the treatment spectrum is poorly understood and described and this may result in patients being left untreated. We hope that with additional epidemiological investigation we will be able to offer a more “risk adapted” approach with more intensive screening and support being offered to individuals who are most at risk of psychological morbidity which may in part be related to their current stage of treatment. This is important as research suggests that cancer patients who are suffering from clinical depression and anxiety are less likely to adhere to their treatment plan and are more likely to experience adverse reactions to their treatment (4,5,35). Consequently, the identification, treatment and management concurrent

psychological distress should be a key clinical objective as a means of enhancing both clinical outcomes and patient quality of life.

There are several limitations to the results generated by this review that need to be noted when interpreting the findings. There is a noticeable dearth of research into the prevalence of depression and anxiety in PCa patients with metastatic disease; we identified only 87 patients with metastatic PCa, out of the pooled sample size of 4494. Given the increased physical symptomology, and significantly lowered life expectancy, associated with metastatic PCa, it is possible that the prevalence of psychological morbidity within this patient cohort will probably be substantially higher. This potential bias is almost certainly a consequence of the sampling frames used by the studies entered into this meta-analysis.

We do not know the overall proportion of men who suffer from some psychological distress during their PCa cancer journey from these largely cross-sectional studies. We suspect that a number of individuals become depressed and anxious at various stages of their cancer journey and then may improve so overall the numbers of people affected at some stage may be higher than we are able to identify from this analysis. We would need to conduct a sustained longitudinal cohort study to resolve this question.

We were also not able to determine whether the prevalence of depression and anxiety was a factor influencing the type of PCa treatments provided to individuals. The associated side effects of PCa treatment include debilitating urinary, sexual and bowel dysfunction as well as the potentially negative psychological side effects of passive treatment options such as active surveillance (AS) and watchful waiting (WW), in which the patient faces living with a diagnosed but untreated cancer. This is an important clinical issue as it may provide a novel avenue in which to streamline the screening of depression and anxiety by offering patients undertaking treatments that have been shown to induce higher rates of distress with early, preventive support during their cancer journey.

Burnett et al (2007) reports that the prevalence of depression among AS/WW patients is just 4% (in a sample of 100 patients recruited from a single cancer centre of international excellence), leading the authors to conclude that AS does not predispose patients to higher levels of distress in comparison to those undergoing radical treatment. However our data identified that the prevalence of depression is almost three times higher than that reported by Burnett at 11% (34) within this specific population, suggesting that psychological distress may indeed be a substantial risk associated with AS/WW.

The utilisation and uptake of AS/WW within the UK is increasing (36), yet our results clearly highlight that the issue of psychological morbidity among these PCa patients is poorly described and defined, with only 4 of the 27 studies entered into this review obtaining measures of depression and anxiety from this patient population (22,23,27,34). Consequently we suggest that patients being treated with AS/WW should be investigated in more detail to better understand the psychological ramifications of this form of management. Such research should ideally involve the recruitment of larger sample sizes (>200) from multiple sites to provide a more generalisable estimate of psychological distress from this patient cohort.

In conclusion, across the treatment spectrum, PCa patients appear to experience a moderate to high degree of psychological morbidity ranging from 15% to 27%. Most acute prevalences of depression and anxiety occur prior to and after the completion of treatment, the consequences of which may go on to negatively impact upon treatment compliance (6), increased periods of hospitalisation (5) and overall functional quality of life (35). Based on our findings we conclude that the assessment, diagnosis and treatment of depression and anxiety should be a key priority for any clinical oncology team working with PCa to enable them to optimise their patients' quality of life and clinical treatment outcomes.

Authors Contribution

Sam Watts: Protocol development, data searching, extraction and analysis and author

Dr Geraline Leydon: Co-author and academic supervisor

Mr Brian Birch: Co-author

Professor Philip Prescott: Statistical analysis

Mrs Lily Lia: Data extraction

Dr Susan Eardley: Data extraction

Professor George Lewith: Co-author and academic supervisor

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Tables

Table 1: Overview of Study Characteristics

	All studies	Pre-Treatment Studies	On-Treatment Studies	Post-Treatment Studies
Study Samples (patient numbers)	4494	1707	723	3087
Participant Ages	66.3 (3.3)	64.8 (2.9)	67.6 (3.3)	66.9 (2.4)
Number of patients with localised PCa	3270	1299	563	2236
Number of patients with advanced PCa	513	162	72	441
Number of patients with metastatic PCa	87	58	40	7

Table 2. The number of PCa patients being treated and undertaking each treatment modality

Radical Prostatectomy	Radiotherapy (EBRT & Brachytherapy)	Hormone Therapy (orchiectomy and ADT)	Chemotherapy	Active Surveillance or Watchful Waiting	Newly diagnosed (no treatment yet selected)
924	1578	264	24	418	304

Table 3. Questionnaires utilised and frequency of use

Questionnaire Name	Frequency of Use
Hospital Anxiety and Depression Scale (HADS)	13
Beck Depression Inventory (BDI)	6
Self Rating Anxiety Scale (SAS)	4
Self Rating Depression Scale (SDS)	4
Centre for Epidemiologic Studies Depression Scale (CES-D)	4
Stait-Trait Anxiety Scale (STAI)	4
Memorial Anxiety Scale for Prostate Cancer (MAX-PC)	3

Figure 1: PRISMA 2009 Flow Diagram

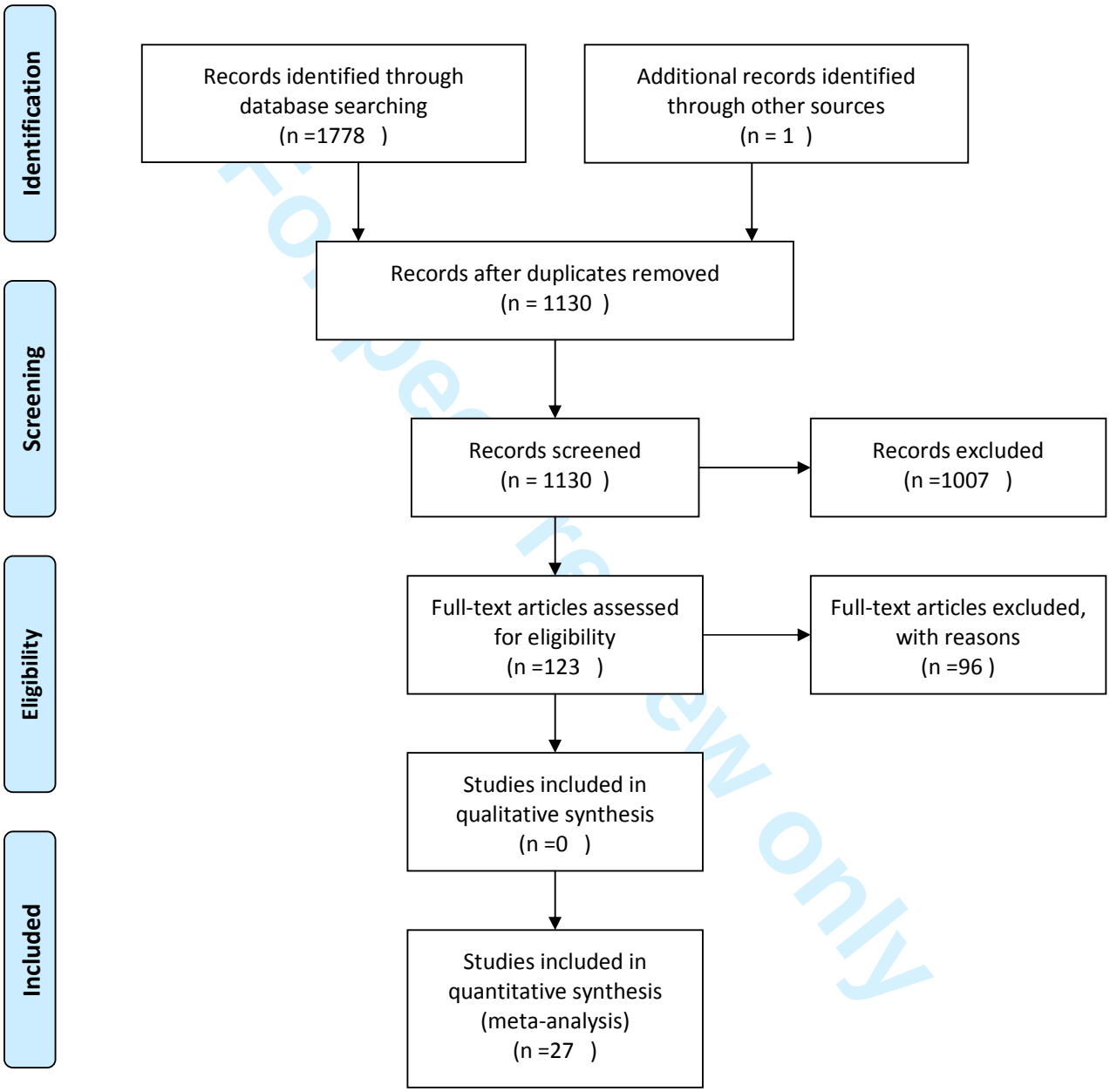


Figure 2: Pre-Treatment Depression and Anxiety Incidence

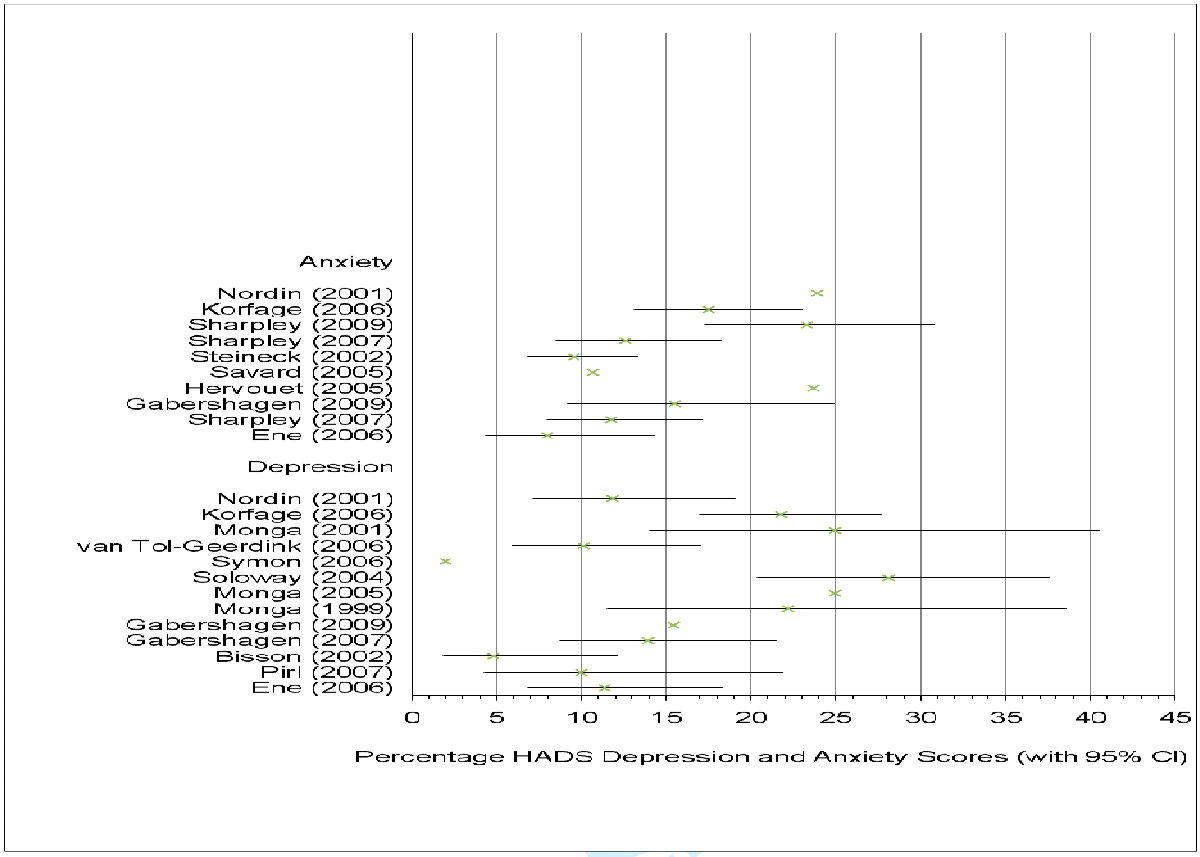


Figure 3: On-treatment Depression and Anxiety Incidence

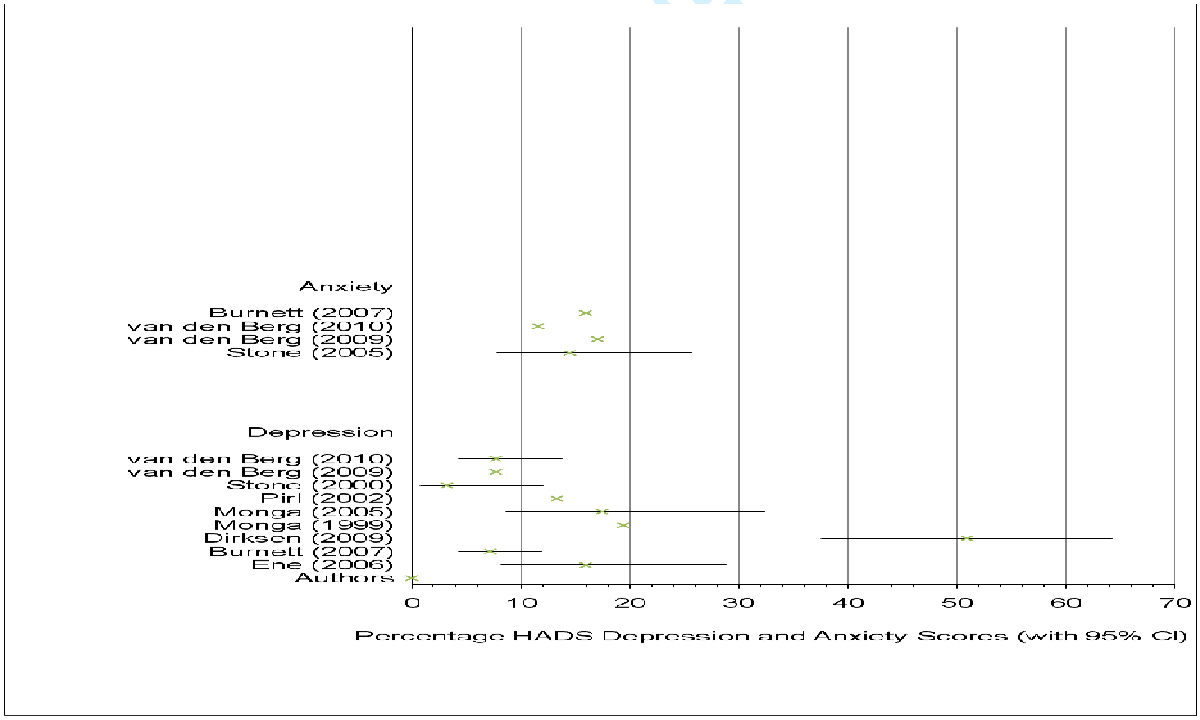


Figure 4: Post Treatment Depression and Anxiety Incidence

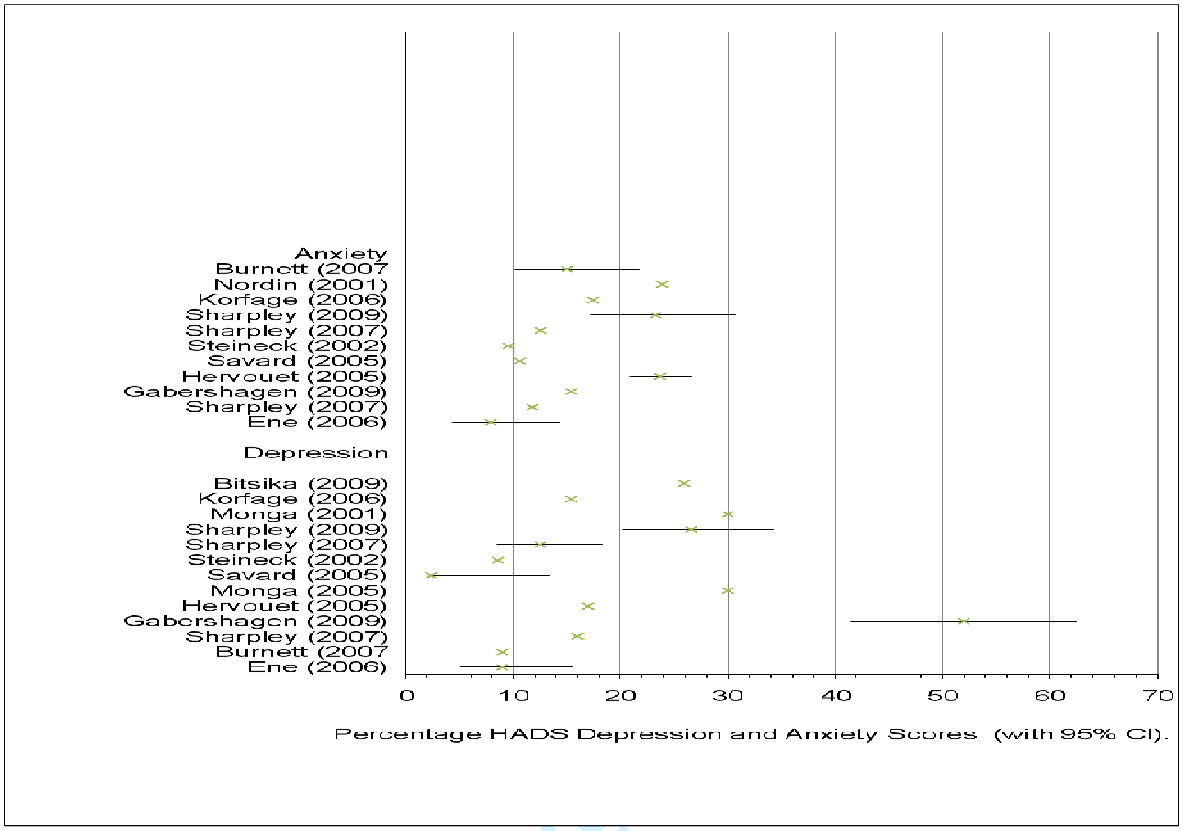
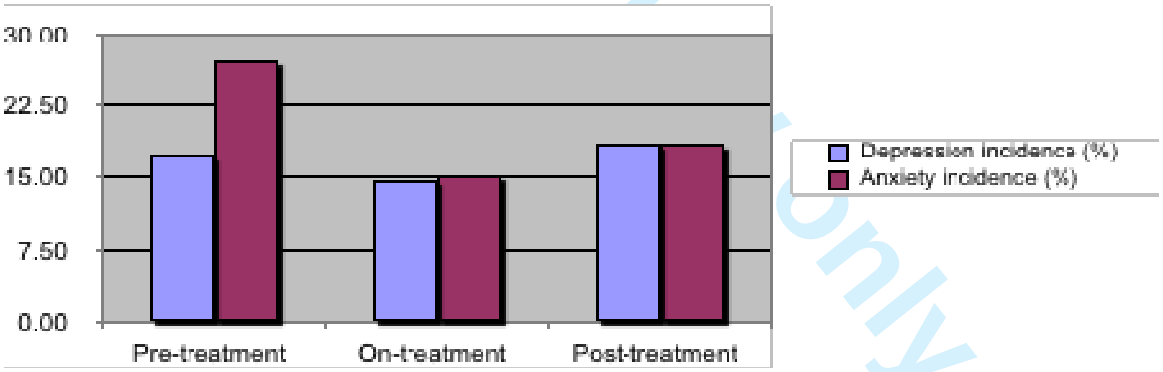


Figure 5: Depression and Anxiety Incidence Across and Within Treatment Groups



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
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	NA
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
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.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
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).	6
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.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
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.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
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.	7

PRISMA 2009 Checklist

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).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
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.	7
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.	8-9
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).	NA
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.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
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).	12
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).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
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.	3

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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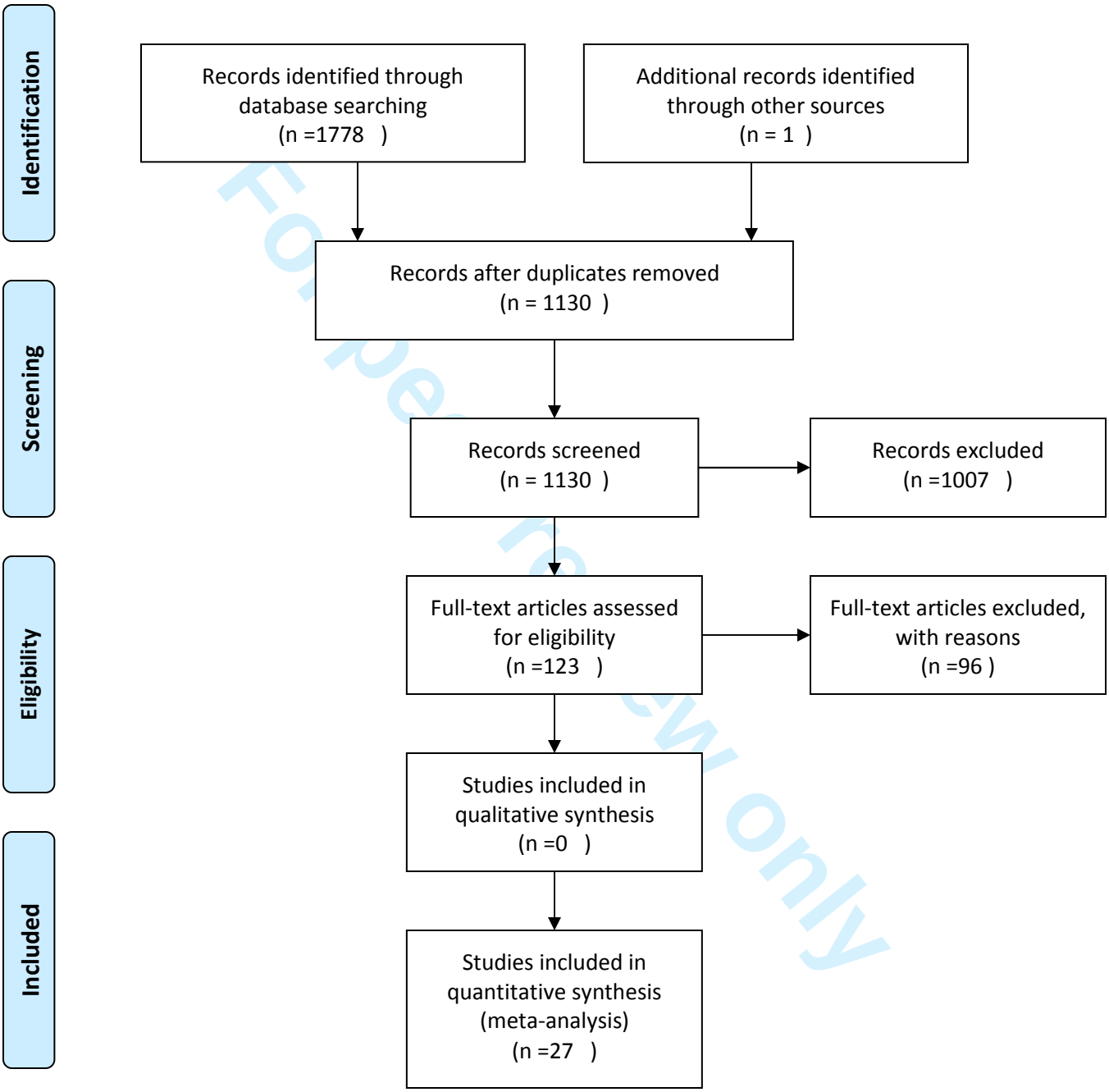
PRISMA 2009 Flow Diagram



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Depression and Anxiety in Prostate Cancer: A Systematic Review and Meta-Analysis of Prevalence Rates

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Depression and Anxiety in Prostate Cancer: A Systematic Review and Meta-Analysis of Prevalence Rates

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Word Count: 3677

Abstract

Objectives: To systematically review the literature pertaining to the prevalence of depression and anxiety in prostate cancer patients as a function of treatment stage.

Design: Systematic review and meta-analysis

Participants: 4494 prostate cancer patients from primary research investigations.

Primary Outcome Measure: The prevalence of clinical depression and anxiety in prostate cancer patients as a function of treatment stage

Results: We identified 27 full journal articles that met the inclusion criteria for entry into the meta-analysis resulting in a pooled sample size of 4494 patients. The meta-analysis of prevalence rates identified pre-treatment, on-treatment and post-treatment depression prevalences of 17.27% (95% CI: 15.06%-19.72%), 14.70% (95% CI: 11.92%-17.99%) and 18.44% (95% CI: 15.18%-22.22%) respectively. Pre-treatment, on-treatment and post-treatment anxiety prevalences were 27.04% (95% CI: 24.26%-30.01%), 15.09% (95% CI: 12.15%-18.60%) and 18.49% (95% CI: 13.81%-24.31%) respectively.

Conclusions: Our findings suggest that the prevalence of depression and anxiety in men with prostate cancer, across the treatment spectrum, are relatively high relatively high.. In light of the growing emphasis placed on cancer survivorship we consider that further research within this area is warranted to ensure psychological distress in prostate cancer patients is not under-diagnosed and under-treated.

Article Summary

Article Focus:

- Identifying systematically how the prevalence of anxiety and depression in men with prostate cancer varies across the treatment trajectory, from pre-treatment to post-treatment follow up

Key Messages:

- Prostate cancer patients display a significantly higher prevalence of depression and anxiety than the normal population across the treatment spectrum, particularly prior to and after the completion of treatment.
- This has important implications for decision making, quality of life and survivorship in this population.
- Further research is required to ensure that psychological distress in men with prostate cancer is clearly identified and managed appropriately

Strengths and Limitations:

- This is the first meta-analysis to define depression and anxiety prevalence specifically within prostate cancer

- Limited data is available for patients on active surveillance and with metastatic disease.
- Cross-sectional methodologies make it difficult to draw definitive conclusions about the history and progression of anxiety and depression over the cancer journey in this population.

Funding Statement

This work was supported by the National Institute for Health Research School of Primary Care Research, grant number 73

Competing Interests: None declared.

Introduction

Prostate cancer (PCa) represents the most common form of non-cutaneous malignancy diagnosed in British men (1). Over 36,000 new cases were diagnosed in 2007, accounting for almost 25% of the total yearly number of male cancer diagnoses (1). With an ageing UK population and increasing utilisation of PCa screening in asymptomatic men (2) the incidence rates of PCa are predicted to continue increasing year on year (1).

In light of such a substantial and sustained disease burden the management of survivorship issues within PCa becomes of paramount importance. Such issues revolve around the effective maintenance of quality of life (QoL) throughout the cancer journey, from initial diagnosis through to post-treatment survivorship. Additionally, the National Cancer Survivorship Initiative (NCSI) established five key goals of improved, personalized and patients centred care in the UK. One goal was the need to better address the specific psychological concerns associated with the diagnosis and treatment of cancer.

Depression and anxiety are two of the most commonly experienced psychological conditions experienced by cancer patients (4) and are associated with unique psycho-physiological side effects that importantly encompass poorer treatment outcomes (6), increased periods of hospitalisation (5) and higher mortality rates (7). With the advances in treatment efficacy, cancer is being increasingly viewed and treated as a chronic disease that can be effectively managed for many years. Given the longevity associated with the trajectory of PCa (over 70% of PCa patients can expect to live for ten years or more from the time of diagnosis) it is possible that the onset of psychological distress within this population of men is not an acute threat that quickly passes but a chronic one with peaks and troughs of severity that occur at key stages of the cancer journey.

The research base evaluating the prevalence of depression and anxiety within PCa is growing steadily and a sizeable body of clinically relevant research currently exists. Unfortunately much of this data is very heterogeneous and of poor methodological quality and has yet to be subjected to rigorous systematic review and meta-analysis. This lack of synthesis makes it very difficult for physicians and allied health care professionals working with PCa to access, interpret and apply the key research findings to their clinical practice.

It is as yet unclear what stages of the PCa cancer journey patients find most distressing. Were this known, or at least better understood, it would allow health care professionals to be more proactive and aware of what stages of treatment patients are most likely to experience

depression and anxiety. This would allow health care teams to risk adapt their psychological screening and support processes.

The current meta-analysis was undertaken to address this issue and provide an initial baseline estimate of the incidence of clinical depression and anxiety in PCa patients during each of the three key stages of cancer treatment; pre-treatment, on-treatment and post-treatment.

Method

Eligibility Criteria

Studies that investigated the specific prevalence of depression and anxiety in prostate cancer (PCa) patients in full journal articles were included. Studies published in conference proceedings, qualitative research, commentaries and discussions, letters, books, book chapters or research not published in the English language were excluded.

Eligible studies were restricted to research focusing on individuals with a biopsy confirmed diagnosis of PCa. If PCa patients were included within an investigation that recruited mixed cancer populations, the study was required to have reported data about the PCa patients as a distinct sub-sample. The primary outcome for the current meta-analysis was the prevalence of depression and anxiety. Thus inclusion into the meta-analysis was restricted to those studies that reported PCa specific prevalence data for depression and anxiety separately.

To be eligible for inclusion, each study was required to provide a clear definition of the PCa treatments undertaken by the study participants and when such treatments took place (i.e. treatment that was yet to be undertaken, was being undertaken at the time of the study or had already been completed. For the latter category, it was a requirement that the authors specified the time lapse since the cessation of treatment).

Questionnaire Analysis

Entry into the meta-analysis was also restricted to data that was collected from questionnaires that provided specific, valid and reliable measurements of depression and anxiety. To enable this, a series of questionnaire specific inclusion criteria were created against which all of the questionnaires utilised in the studies could be assessed; each questionnaire must:

1. Allow for the specific and independent measurement of depression and anxiety.

2. Have available established threshold information (measurements) for the diagnosis of depression and anxiety.

3. The validity of each questionnaire must have been assessed in comparison to established “gold standard” questionnaires.

4. The internal validity and reliability of each questionnaire must have been assessed and deemed acceptable (test-retest).

Twelve questionnaires meeting the criteria were identified which included the Hospital Anxiety and Depression Scale, Stait -Trait Anxiety Scale, Centre for Epidemiologic Studies Depression Scale, Symptom Checklist, Beck Depression Inventory, Self-Rating Anxiety Scale, Self-Rating Depression Scale, Brief Symptom Inventory, Composite International Diagnostic Interview, Memorial Anxiety Scale for Prostate Cancer and the Effects of Prostate Cancer on Lifestyle Questionnaire

Identifying Research Evidence

Data searches were conducted between June 2011 and August 2011. The search protocol was subsequently re-run in June 2013 to ensure no additional data were identified. We searched 6 electronic databases (OVID Medline, EMBASE, AMED, PsycINFO, CINAHL and Web of Science) for articles that met the previously discussed criteria using pre-specified MESH terms as that included Prostate Neoplasm (EXP)” OR “Prostate Cancer” AND “Depression (EXP)” or “Anxiety (EXP)” or “Psychological distress (EXP” or “Stress (EXP)” or “Distress (EXP)”.

To supplement the electronic searches we also conducted searches of the reference lists of previous reviews, key papers and other relevant articles identified by the electronic search. We also conducted systematic searches of the content lists of key journals to identify any additional studies missed by the electronic search.

Study Selection

Titles and abstracts were initially assessed for eligibility. If it was possible to confirm that an article met the inclusion criteria from the abstract alone, the full text article was retrieved. If it was clear from the abstract that an article was not eligible, it was rejected immediately. If it was not possible to determine the eligibility of an article from the abstract, the full text article

was retrieved. If any key information was missing, we contacted the authors for the missing data. If this was not possible or ineffective, the study was rejected, (see Figure 1).

Data Extraction

The following specific information relating to data collection and results was extracted individually from each identified article and entered into a pre-designed Excel spread sheet: date and geographical location of data collection; aims and objectives of the investigation; study design; participant inclusion and exclusion criteria; recruitment procedures; sample size; disease stage; socio-demographic status (age, ethnicity and relationship, educational and employment status); time since diagnosis; additional co-morbidity; stage of treatment (pre, on or post-treatment); treatments undertaken (surgery, radiotherapy, hormone therapy, chemotherapy, active-surveillance/watchful waiting); questionnaires utilised; statistical analyses performed; depression prevalence (%) and anxiety prevalence (%).

To test the consistency of data extraction across the studies, three researchers (SW, LL, SE) extracted data from the same 6 randomly selected articles then compared the results of their extraction. A points system was utilised to allow for the objective assessment of consistency. 1 point was allocated for variables with identical data extraction and 0 points for variables with differences. Across all ratings, consistency ranged from 92% to 96% (median: 94%).

Meta-Analysis Procedure

Given the range of estimated proportions expected within the extracted data, the logits of proportions method of conducting the statistical analysis was employed, rather than utilising normal approximations of binomial distributions.

Cochran's Q test was applied to the logits to test the hypothesis of homogeneity of the within study estimates of the proportions, with larger Q values suggesting that the estimates are not homogeneous. Initial analyses highlighted Q values between Q= 15.2 and 215, with some of the larger values suggesting a degree of heterogeneity, the result in some cases of only one or two studies being out of line with the others. For completeness, meta-analysis results have been provided even for those cases where heterogeneity is evident.

Results

Search Results

The electronic database searches initially yielded 1778 journal article references. 1655 of these were subsequently removed due to either duplication or a failure to meet the inclusion criteria. Full text articles were then retrieved and critically appraised for the remaining 123 journal references. Of these 123 articles 97 did not meeting the inclusion criteria. The remaining 26 articles were entered into the meta-analysis.

Hand searches of the key journals identified by the electronic database search revealed no additional journal articles. Searching the reference lists of articles identified through the electronic database search identified 2 journal article references of interest that had otherwise been missed. Full text articles were retrieved for these 2 references, one of which could be included making the total included 27. (Figure 1).

INSERT FIGURE 1

Study Locations

Of the 27 studies entered into the review, 9 were conducted within America (5,8,9,10,12,13,14,15,16), 4 in both Australia (17,18,19,20) and Holland (21,22,23,24), 3 in the UK (25,26,27), 2 each in Sweden (28,29), Germany (30,31) and Canada (32,33) and 1 in Finland (34). An overview of the key features of each of the included studies can be seen in Table 1.

INSERT TABLE 1

Study Sample Sizes

The samples sizes of the studies entered into the review varied widely from 36 to 861. The total sample size across all 27 studies was 4494 with a mean sample size of 158. The sample sizes of the individual treatment stage groups (pre, on and post-treatment) can be seen in Table 2.

Participant Age

Data on participant age was reported by 24 of the 27 studies and in all 24 cases mean age was reported. The range of mean ages across the 24 studies varied from 57.5 years to 73.2 years. The mean age of all participants across the 24 studies was 66.3 years (3.3). Three studies failed to report participant age in any format. The mean age of the participants in each of the three treatment groups can be seen in Table 2.

Cancer Staging

Data regarding participant cancer stage was reported by 23 of the 27 studies. There was a general lack of consistency regarding reporting methods. Several studies utilised the clinical T-staging system of T1 (localised) to T4 (metastatic) whilst the majority simply graded PCa as localised, advanced or metastatic. No study reported patient disease stage using the recommended tumour-nodes-metastasis (TNM). The majority of patients had been diagnosed with localised disease (n=3270), followed by advanced (513) and metastatic PCa (87), as shown in Table 2.

INSERT TABLE 2

Cancer Treatments Undertaken

Table 3 provides an overview of the number of participants undergoing each PCa treatment. Unfortunately, it was not possible to stratify the treatments undertaken as a function of either disease stage (localised, advanced or metastatic) or treatment stage (on-treatment or post-treatment). This was because in many instances patients with different disease staging or who were at different treatment stages were recruited into the same cohort. Consequently, whilst the number of patients completing each type of treatment was clearly highlighted, it was not possible to determine whether the patients with localized, advanced or metastatic disease, nor those who were either on or post-treatment, had completed them. Thus the data in Table 3 provides a collective overview of the treatments undertaken by all of the patients, irrespective of disease or treatment stage. Additionally, several of the pre-treatment studies recruited participants who had yet to decide upon treatment. Such patients are listed in Table 3 as ‘newly diagnosed’.

INSERT TABLE 3

2.6. Questionnaires Analysis

Of the 12 questionnaires meeting the questionnaire inclusion criteria as listed in the method section, only 7 were utilised by the 27 studies entered into this meta-analysis. Table 4 lists the 7 questionnaires, the frequency with which they were used and the clinical cut-off scores utilized to determine caseness.

INSERT TABLE 4

Meta-Analysis of Depression and Anxiety Prevalence

Number of studies reporting depression

26 of the 27 studies entered into the review reported data on depression prevalence. Of these 26, 13 reported depression in pre-treatment patients, 9 in on-treatment patients, and 13 in post-treatment patients. The number of total studies from the 3 groups exceeded 27 as several longitudinal studies reported depression in multiple treatment groups (i.e. in both pre-treatment and on-treatment groups).

Number of studies reporting anxiety

20 of the 26 studies entered into the review reported data on anxiety prevalence. Of these 20, 9 reported anxiety in pre-treatment patients, 4 in on-treatment patients and 11 in post-treatment patients.

Number of Patients Measured for Depression

Collectively, measures of depression were recorded from 5139 participants across the 26 studies. In terms of the individual treatment groups, 1259 participants provided measures of depression in the pre-treatment group, 723 in the on-treatment group and 3157 in the post treatment group.

Number of Patients Measured for Anxiety

Collectively, measures of anxiety were recorded from 4635 participants across the 20 studies. In terms of the individual treatment groups, 1057 participants provided measures of anxiety in the pre-treatment group, 501 in the on-treatment group and 3077 in the post treatment group.

Pre-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of depression was 17.27% (CI: 15.06%-19.72%).

Anxiety: Within the 9 studies that provided measures of anxiety in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of anxiety was 27.04% (CI: 24.26%-30.01%).

INSERT FIGURE 2

On-Treatment Depression and Anxiety Prevalence

Depression: Within the 9 studies that provided measures of depression in PCa patients currently undergoing treatment (see Figure 2), the prevalence of depression was 14.70% (CI: 11.92%-17.99%).

Anxiety: Within the 4 studies that provided measures of anxiety in PCa patients currently undergoing treatment (see Figure 2), the prevalence of anxiety was 15.09% (CI: 12.15%-18.60%).

INSERT FIGURE 3

Post-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients who had completed treatment (see Figure 3), the prevalence of depression was 18.44% (CI: 15.18%-22.22%).

Anxiety: Within the 11 studies that provided measures of anxiety in PCa patients who had completed treatment (see Figure 3), the prevalence of anxiety was 18.49% (CI: 13.81%-24.31%).

INSERT FIGURE 4

Depression and Anxiety Prevalence Across and Within Treatment Groups

Figure 4 provides a pictorial representation of the prevalence of depression and anxiety both within and across each of the three treatment groups.

INSERT FIGURE 5

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Discussion

There is a real need within clinical oncology, particularly as the burden of disease is escalating with improved diagnosis and treatment, for an increased awareness about the issue of psychological distress among men diagnosed with, being treated for and surviving through/living with a PCa diagnosis. The results of the current meta-analysis go some way in addressing this issue by providing those working within the field of PCa with a rigorous overview of the likely prevalence of depression and anxiety in the patients they treat. Our findings suggest that over the trajectory of the PCa journey, depression and anxiety prevalence are highest in patients who have yet to undergo treatment (17.27% and 27.4% respectively), lowest in patients who are currently undertaking treatment (14.70% and 15.90% respectively) before rising again in patients who have completed treatment (18.44% and 18.49% respectively). The relatively small variation observed within these prevalence rates across the different treatment stages, along with the large collective sample size of the

meta-analysis (4494) suggests these conclusions are valid powerful and robust summaries of the data available. The prevalence of clinical depression and anxiety in British men aged over 65 years is estimated to be less than 9% and 6%, respectively (35). Such data are in stark contrast to the prevalence reported in PCa patients of the same age in this study.

The current meta-analysis is the first of its kind to specifically assess the prevalence of clinical depression and anxiety in prostate cancer (PCa) patients over their treatment spectrum, from pre-treatment, through treatment to post-treatment follow up. To date, the lack of synthesis of the available data relating to depression and anxiety in PCa has meant that clinical decisions have been based on isolated research trials that lack sufficient power and depth in terms of sample sizes, treatment protocols and treatment stages. Consequently the true prevalence of psychological morbidity experienced by PCa patients across the treatment spectrum is poorly understood and described and this may result in patients being left untreated. We hope that with additional epidemiological investigation we will be able to offer a more risk adapted approach with more intensive screening and support being offered to individuals who are most at risk of psychological morbidity which may in part be related to their current stage of treatment. This is important as research suggests that cancer patients who are suffering from clinical depression and anxiety are less likely to adhere to their treatment plan and are more likely to experience adverse reactions to their treatment (4,5). Consequently, the identification, treatment and management concurrent psychological distress should be a key clinical objective as a means of enhancing both clinical outcomes and patient quality of life.

There are several limitations to the results generated by this review that need to be noted when interpreting the findings. There is a noticeable dearth of research into the prevalence of depression and anxiety in PCa patients with metastatic disease; we identified only 87 patients with metastatic PCa, out of the pooled sample size of 4494. Given the increased physical symptomology, and significantly lowered life expectancy, associated with metastatic PCa, it is possible that the prevalence of psychological morbidity within this patient cohort will probably be substantially higher. . Unfortunately it was not possible to generate depression and anxiety prevalence data specifically for men with metastatic disease as the studies that recruited PCa patients with metastatic disease did so as part of larger collective samples of patients that included those with localised and/or advanced PCa. In the majority of cases, no individual depression and anxiety data was provided specifically for those with metastatic disease. Consequently it was not possible to describe these patients separately.

We do not know the overall proportion of men who suffer from some psychological distress during their PCa cancer journey from these largely cross-sectional studies. We suspect that

a number of individuals become depressed and anxious at various stages of their cancer journey and then may improve so overall the numbers of people affected at some stage may be higher than we are able to identify from this analysis. We would need to conduct a sustained longitudinal cohort study to resolve this question. Likewise, none of the included studies provided any form of data relating to the patients past history of depression and anxiety. Consequently it was not possible to determine whether a past history of depression and anxiety acted as a significant predictor of current depression and anxiety.

It is also important to note the wide variability in both the point prevalence estimates of anxiety and depression and the 95% confidence intervals associated with them. There are likely to be many reasons for this variability which include sample size, selective populations and the differing instruments that have been used to measure depression and anxiety. Unfortunately it was not possible to formally investigate the properties of the populations to determine whether there were any differences that would explain this variability. It is important that furture studies into the assessment of depression and anxiety in this patient group carefully identidy the characterisitcs of their populations to address this issue.

We were also not able to determine whether the prevalence of depression and anxiety was a factor influencing the type of PCa treatments provided to individuals. The associated side effects of PCa treatment include debilitating urinary, sexual and bowel dysfunction as well as the potentially negative psychological side effects of passive treatment options such as active surveillance (AS) and watchful waiting (WW), in which the patient faces living with a diagnosed but untreated cancer. This is an important clinical issue as it may provide a novel avenue in which to streamline the screening of depression and anxiety by offering patients undertaking treatments that have been shown to induce higher rates of distress with early, preventive support during their cancer journey.

Burnett et al (2007) reports that the prevalence of depression among AS/WW patients is just 4% (in a sample of 100 patients recruited from a single cancer centre of international excellence), leading the authors to conclude that AS does not predispose patients to higher levels of distress in comparison to those undergoing radical treatment. However our data identified that the prevalence of depression is almost three times higher than that reported by Burnett et al (2007) at 11% (within this specific population, suggesting that psychological distress may indeed be a substantial risk associated with AS/WW.

The utilisation and uptake of AS/WW within the UK is increasing (36), yet our results clearly highlight that the issue of psychological morbidity among these PCa patients is poorly described and defined, with only 4 of the 27 studies entered into this review obtaining measures of depression and anxiety from this patient population (22,23,27,34).

Consequently we suggest that patients being treated with AS/WW should be investigated in more detail to better understand the psychological ramifications of this form of management. Such research should ideally involve the recruitment of larger sample sizes (>200) from multiple sites to provide a more generalisable estimate of psychological distress from this patient cohort.

In conclusion, across the treatment spectrum, PCa patients appear to experience a moderate to high degree of psychological morbidity ranging from 15% to 27%. Most acute prevalences of depression and anxiety occur prior to and after the completion of treatment, the consequences of which may go on to negatively impact upon treatment compliance (6), increased periods of hospitalisation (5) and overall functional quality of life (37). Based on our findings we conclude that the assessment, diagnosis and treatment of depression and anxiety should be a key priority for any clinical oncology team working with PCa to enable them to optimise their patients' quality of life and clinical treatment outcomes.

Authors Contribution

Sam Watts: Protocol development, data searching, extraction and analysis and author

Dr Geraline Leydon: Co-author and academic supervisor

Mr Brian Birch: Co-author

Professor Philip Prescott: Statistical analysis

Mrs Lily Lia: Data extraction

Dr Susan Eardley: Data extraction

Professor George Lewith: Co-author and academic supervisor

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Tables

Table 1: Key features of the included studies

Author	Year	Location	Sample size	Participant Age	Cancer stage	Treatment stage
Ene	2006	Sweden.	123	63.1	No data provided	Pre to Post-treatment
Pirl	2008	USA.	50	62	Advanced	Pre and On-treatment
Sharpley	2007	Australia.	195	69.2	Localised	Post-treatment
Bisson	2002	Wales	83	64.5	Mixed	Pre-treatment
Dirkson	2009	USA	51	73.4	Mixed	On-treatment
Dale	2009	USA	67	67.9	No data provided	Pre-treatment (but all participants had received prior primary therapy)
Gabershagen	2007	Germany	115	64.1	Localised	Pre-treatment
Gabershagen	2009	Germany	84	62.8	Mixed	Pre-treatment to post-treatment
Hervouet	2005	Canada	861	67.9	Mixed	Post-treatment
Monga	1999	USA	36	66	Localised	Pre-treatment to On-treatment to Post treatment
Monga	2005	USA	40	67.8	Localised	Pre-treatment to On-treatment to Post-treatment
Pirl	2002	USA	45	69.4	Localised and Metastatic	On-treatment
Savard	2005	Canada	327	66	localised	Post-treatment
Stone	2000	England.	62	69	Mixed	On-treatment
Soloway	2004	USA	103	62	No data provided	Pre-treatment
Steineck	2002	Finland	326	64.5	Localised	Post-treatment
Symon	2006	USA	50	59.9	Localised	Pre-treatment to Post-treatment
Sharpley	2007	Australia.	183	69.2	Localised	Post-treatment
Sharpley	2009	Australia.	150	69.8	Localised	Post-treatment
van Tol-Geerdink	2006	Holland	118	70	Localised	Pre-treatment
Van den Berg	2009	Holland	129	64.9	Localised	On-treatment (active surveillance)
Van den Berg	2010	Holland	129	64.6	Localised	On-treatment (active surveillance)
Monga	2001	USA	40	67.6	Localised	Pre-treatment to Post-treatment
Korfage	2006	Holland	299	65.4	Mixed	Pre-Post treatment
Bitsika	2009	Australia	381	No data	Localised	Post-treatment
Nordin	2001	Sweden	118	No data	Localised & Advanced	Pre-treatment
Burnett	2007	England	329	68.8	Localised	On-treatment and post-treatment

Table 2: Overview of Study Characteristics

	All studies	Pre-Treatment Studies	On-Treatment Studies	Post-Treatment Studies
Study Samples (patient numbers)	4494	1707	723	3087
Participant Ages	66.3 (3.3)	64.8 (2.9)	67.6 (3.3)	66.9 (2.4)
Number of patients with localised PCa	3270	1299	563	2236
Number of patients with advanced PCa	513	162	72	441
Number of patients with metastatic PCa	87	58	40	7

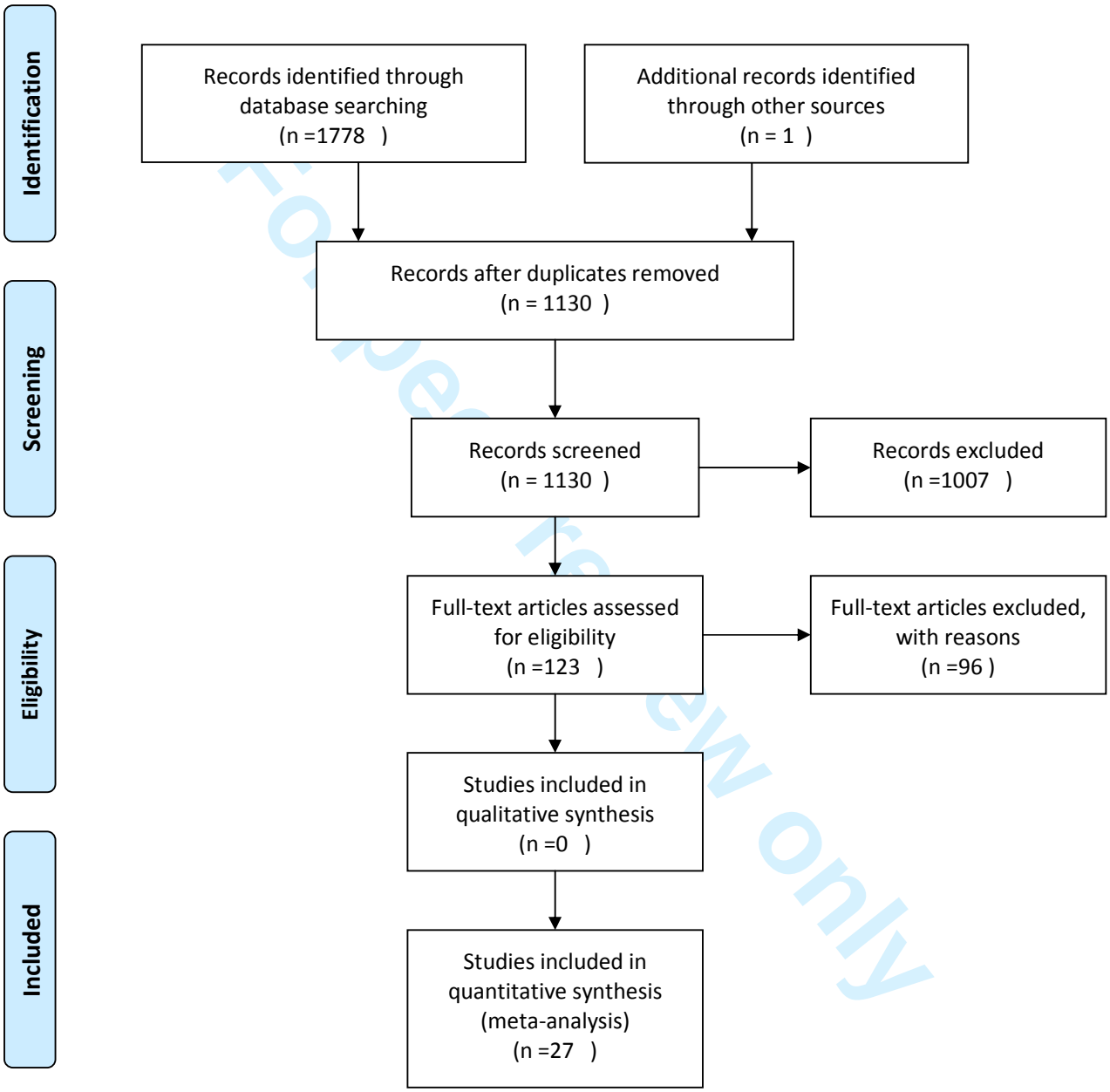
Table 3. The number of PCa patients being treated and undertaking each treatment modality

Radical Prostatectomy	Radiotherapy (EBRT & Brachytherapy)	Hormone Therapy (orchiectomy and ADT)	Chemotherapy	Active Surveillance or Watchful Waiting	Newly diagnosed (no treatment yet selected)
924	1578	264	24	418	304

Table 4. Questionnaires utilised , frequency of use and cut-off scores utilized

Questionnaire Name	Frequency of Use	Clinical Cut-Off Scores Utilised
Hospital Anxiety and Depression Scale (HADS)	13	HADS-A: ≥8 HADS-D: ≥8
Beck Depression Inventory (BDI)	6	≥10
Self Rating Anxiety Scale (SAS)	4	≥36
Self Rating Depression Scale (SDS)	4	≥40
Centre for Epidemiologic Studies Depression Scale (CES-D)	4	≥15
Stait-Trait Anxiety Scale (STAI)	4	≥44
Memorial Anxiety Scale for Prostate Cancer (MAX-PC)	3	≥27

Figure 1: PRISMA 2009 Flow Diagram



Depression and Anxiety in Prostate Cancer: A Systematic Review and Meta-Analysis of Prevalence Rates

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Abstract

Objectives: To systematically review the literature pertaining to the prevalence of depression and anxiety in prostate cancer patients as a function of treatment stage.

Design: Systematic review and meta-analysis

Participants: 4494 prostate cancer patients from primary research investigations.

Primary Outcome Measure: The prevalence of clinical depression and anxiety in prostate cancer patients as a function of treatment ~~statge~~stage

Results: We identified 27 full journal articles that met the inclusion criteria for entry into the meta-analysis resulting in a pooled sample size of 4494 patients. The meta-analysis of prevalence rates identified pre-treatment, on-treatment and post-treatment depression prevalences of 17.27% (95% CI: 15.06%-19.72%), 14.70% (95% CI: 11.92%-17.99%) and 18.44% (95% CI: 15.18%-22.22%) respectively. Pre-treatment, on-treatment and post-treatment anxiety prevalences were 27.04% (95% CI: 24.26%-30.01%), 15.09% (95% CI: 12.15%-18.60%) and 18.49% (95% CI: 13.81%-24.31%) respectively.

Conclusions: Our findings suggest that the prevalence of depression and anxiety in men with prostate cancer, across the treatment spectrum, are relatively high relatively high. ~~and in keeping with that observed in other cancer sites~~. In light of the growing emphasis placed on cancer survivorship we consider that further research within this area is warranted to ensure psychological distress in prostate cancer patients is not under-diagnosed and under-treated.

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Article Summary

Article Focus:

- Identifying systematically how the prevalence of anxiety and depression in men with prostate cancer varies across the treatment trajectory, from pre-treatment to post-treatment follow up

Key Messages:

- Prostate cancer patients display a significantly higher prevalence of depression and anxiety than the normal population across the treatment spectrum, particularly prior to and after the completion of treatment.
- This has important implications for decision making, quality of life and survivorship in this population.
- Further research is required to ensure that psychological distress in men with prostate cancer is clearly identified and managed appropriately

Strengths and Limitations:

- This is the first meta-analysis to define depression and anxiety prevalence specifically within prostate cancer

- Limited data is available for patients on active surveillance and with metastatic disease.
- Cross-sectional methodologies make it difficult to draw definitive conclusions about the history and progression of anxiety and depression over the cancer journey in this population.

Funding Statement

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Competing Interests: None declared.

Introduction

Prostate cancer (PCa) represents the most common form of non-cutaneous malignancy diagnosed in British men (1). Over 36,000 new cases were diagnosed in 2007, accounting for almost 25% of the total yearly number of male cancer diagnoses (1). With an ageing UK population and increasing utilisation of PCa screening in asymptomatic men (2) the incidence rates of PCa are predicted to continue increasing year on year (1).

In light of such a substantial and sustained disease burden the management of survivorship issues within PCa becomes of paramount importance. Such issues revolve around the effective maintenance of quality of life (QoL) throughout the cancer journey, from initial diagnosis through to post-treatment survivorship. Additionally, the National Cancer Survivorship Initiative (NCSI) established five key goals of improved, personalized and patients centred care in the UK. One goal was the need to better address the specific psychological concerns associated with the diagnosis and treatment of cancer.

Depression and anxiety are two of the most commonly experienced psychological conditions experienced by cancer patients (4) and are associated with unique psycho-physiological side effects that importantly encompass poorer treatment outcomes (6), increased periods of hospitalisation (5) and higher mortality rates (7). With the advances in treatment efficacy, cancer is being increasingly viewed and treated as a chronic disease that can be effectively managed for many years. Given the longevity associated with the trajectory of PCa (over 70% of PCa patients can expect to live for ten years or more from the time of diagnosis) it is possible that the onset of psychological distress within this population of men is not an acute threat that quickly passes but a chronic one with peaks and troughs of severity that occur at key stages of the cancer journey.

The research base evaluating the prevalence of depression and anxiety within PCa is growing steadily and a sizeable body of clinically relevant research currently exists. Unfortunately much of this data is very heterogeneous and of poor methodological quality and has yet to be subjected to rigorous systematic review and meta-analysis. This lack of synthesis makes it very difficult for physicians and allied health care professionals working with PCa to access, interpret and apply the key research findings to their clinical practice.

It is as yet unclear what stages of the PCa cancer journey patients find most distressing. Were this known, or at least better understood, it would allow health care professionals to be more proactive and aware of what stages of treatment patients are most likely to experience

depression and anxiety. This would allow health care teams to risk adapt their psychological screening and support processes.

The current meta-analysis was undertaken to address this issue and provide an initial baseline estimate of the incidence of clinical depression and anxiety in PCa patients during each of the three key stages of cancer treatment; pre-treatment, on-treatment and post-treatment.

Method

Eligibility Criteria

Studies that investigated the specific prevalence of depression and anxiety in prostate cancer (PCa) patients in full journal articles were included. Studies published in conference proceedings, qualitative research, commentaries and discussions, letters, books, book chapters or research not published in the English language were excluded.

Eligible studies were restricted to research focusing on individuals with a biopsy confirmed diagnosis of PCa. If PCa patients were included within an investigation that recruited mixed cancer populations, the study was required to have reported data about the PCa patients as a distinct sub-sample. The primary outcome for the current meta-analysis was the prevalence of depression and anxiety. Thus inclusion into the meta-analysis was restricted to those studies that reported PCa specific prevalence data for depression and anxiety separately.

To be eligible for inclusion, each study was required to provide a clear definition of the PCa treatments undertaken by the study participants and when such treatments took place (i.e. treatment that was yet to be undertaken, was being undertaken at the time of the study or had already been completed. For the latter category, it was a requirement that the authors specified the time lapse since the cessation of treatment).

Questionnaire Analysis

Entry into the meta-analysis was also restricted to data that was collected from questionnaires that provided specific, valid and reliable measurements of depression and anxiety. To enable this, a series of questionnaire specific inclusion criteria were created against which all of the questionnaires utilised in the studies could be assessed; each questionnaire must:

1. Allow for the specific and independent measurement of depression and anxiety.

2. Have available established threshold information (measurements) for the diagnosis of depression and anxiety.
3. The validity of each questionnaire must have been assessed in comparison to established “gold standard” questionnaires.
4. The internal validity and reliability of each questionnaire must have been assessed and deemed acceptable (test-retest).

Twelve questionnaires meeting the criteria were identified which included the Hospital Anxiety and Depression Scale, Stait -Trait Anxiety Scale, Centre for Epidemiologic Studies Depression Scale, Symptom Checklist, Beck Depression Inventory, Self-Rating Anxiety Scale, Self-Rating Depression Scale, Brief Symptom Inventory, Composite International Diagnostic Interview, Memorial Anxiety Scale for Prostate Cancer and the Effects of Prostate Cancer on Lifestyle Questionnaire

Identifying Research Evidence

Data searches were conducted between June 2011 and August 2011. The search protocol was subsequently re-run in June 2013 to ensure no additional data were identified. We searched 6 electronic databases (OVID Medline, EMBASE, AMED, PsycINFO, CINAHL and Web of Science) for articles that met the previously discussed criteria using pre-specified MESH terms as that included Prostate Neoplasm (EXP)” OR “Prostate Cancer” AND “Depression (EXP)” or “Anxiety (EXP)” or “Psychological distress (EXP” or “Stress (EXP)” or “Distress (EXP)”.

To supplement the electronic searches we also conducted searches of the reference lists of previous reviews, key papers and other relevant articles identified by the electronic search. We also conducted systematic searches of the content lists of key journals to identify any additional studies missed by the electronic search.

Study Selection

Titles and abstracts were initially assessed for eligibility. If it was possible to confirm that an article met the inclusion criteria from the abstract alone, the full text article was retrieved. If it was clear from the abstract that an article was not eligible, it was rejected immediately. If it was not possible to determine the eligibility of an article from the abstract, the full text article

was retrieved. If any key information was missing, we contacted the authors for the missing data. If this was not possible or ineffective, the study was rejected, (see Figure 1).

Data Extraction

The following specific information relating to data collection and results was extracted individually from each identified article and entered into a pre-designed Excel spread sheet: date and geographical location of data collection; aims and objectives of the investigation; study design; participant inclusion and exclusion criteria; recruitment procedures; sample size; disease stage; socio-demographic status (age, ethnicity and relationship, educational and employment status); time since diagnosis; additional co-morbidity; stage of treatment (pre, on or post-treatment); treatments undertaken (surgery, radiotherapy, hormone therapy, chemotherapy, active-surveillance/watchful waiting); questionnaires utilised; statistical analyses performed; depression prevalence (%) and anxiety prevalence (%).

To test the consistency of data extraction across the studies, three researchers (SW, LL, SE) extracted data from the same 6 randomly selected articles then compared the results of their extraction. A points system was utilised to allow for the objective assessment of consistency. 1 point was allocated for variables with identical data extraction and 0 points for variables with differences. Across all ratings, consistency ranged from 92% to 96% (median: 94%).

Meta-Analysis Procedure

Given the range of estimated proportions expected within the extracted data, the logits of proportions method of conducting the statistical analysis was employed, rather than utilising normal approximations of binomial distributions.

Cochran's Q test was applied to the logits to test the hypothesis of homogeneity of the within study estimates of the proportions, with larger Q values suggesting that the estimates are not homogeneous. Initial analyses highlighted Q values between Q= 15.2 and 215, with some of the larger values suggesting a degree of heterogeneity, the result in some cases of only one or two studies being out of line with the others. For completeness, meta-analysis results have been provided even for those cases where heterogeneity is evident.

Results

Search Results

The electronic database searches initially yielded 1778 journal article references. 1655 of these were subsequently removed due to either duplication or a failure to meet the inclusion criteria. Full text articles were then retrieved and critically appraised for the remaining 123 journal references. Of these 123 articles 97 did not meeting the inclusion criteria. The remaining 26 articles were entered into the meta-analysis.

Hand searches of the key journals identified by the electronic database search revealed no additional journal articles. Searching the reference lists of articles identified through the electronic database search identified 2 journal article references of interest that had otherwise been missed. Full text articles were retrieved for these 2 references, one of which could be included making the total included 27. (Figure 1).

INSERT FIGURE 1

Study Locations

Of the 27 studies entered into the review, 9 were conducted within America (5,8,9,10,12,13,14,15,16), 4 in both Australia (17,18,19,20) and Holland (21,22,23,24), 3 in the UK (25,26,27), 2 each in Sweden (28,29), Germany (30,31) and Canada (32,33) and 1 in Finland (34). An overview of the key features of each of the included studies can be seen in Table 1.

INSERT TABLE 1

Study Sample Sizes

The samples sizes of the studies entered into the review varied widely from 36 to 861. The total sample size across all 27 studies was 4494 with a mean sample size of 158. The sample sizes of the individual treatment stage groups (pre, on and post-treatment) can be seen in Table 2.

Participant Age

Data on participant age was reported by 24 of the 27 studies and in all 24 cases mean age was reported. The range of mean ages across the 24 studies varied from 57.5 years to 73.2 years. The mean age of all participants across the 24 studies was 66.3 years (3.3). Three studies failed to report participant age in any format. The mean age of the participants in each of the three treatment groups can be seen in Table 2.

Cancer Staging

Data regarding participant cancer stage was reported by 23 of the 27 studies. There was a general lack of consistency regarding reporting methods. Several studies utilised the clinical T-staging system of T1 (localised) to T4 (metastatic) whilst the majority simply graded PCa as localised, advanced or metastatic. No study reported patient disease stage using the recommended tumour-nodes-metastasis (TNM). The majority of patients had been diagnosed with localised disease (n=3270), followed by advanced (513) and metastatic PCa (87), as shown in Table 2.

INSERT TABLE 2

Cancer Treatments Undertaken

Table 3 provides an overview of the number of participants undergoing each PCa treatment. Unfortunately, it was not possible to stratify the treatments undertaken as a function of either disease stage (localised, advanced or metastatic) or treatment stage (on-treatment or post-treatment). This was because in many instances patients with different disease staging or who were at different treatment stages were recruited into the same cohort. Consequently, whilst the number of patients completing each type of treatment was clearly highlighted, it was not possible to determine whether the patients with localized, advanced or metastatic disease, nor those who were either on or post-treatment, had completed them. Thus the data in Table 3 provides a collective overview of the treatments undertaken by all of the patients, irrespective of disease or treatment stage. Additionally, several of the pre-treatment studies recruited participants who had yet to decide upon treatment. Such patients are listed in Table 3 as 'newly diagnosed'.

INSERT TABLE 3

2.6. Questionnaires Analysis

Of the 12 questionnaires meeting the questionnaire inclusion criteria as listed in the method section, only 7 were utilised by the 27 studies entered into this meta-analysis. Table 4 lists the 7 questionnaires, the frequency with which they were used and the clinical cut-off scores utilized to determine caseness.

INSERT TABLE 4

Meta-Analysis of Depression and Anxiety Prevalence

Number of studies reporting depression

26 of the 27 studies entered into the review reported data on depression prevalence. Of these 26, 13 reported depression in pre-treatment patients, 9 in on-treatment patients, and 13 in post-treatment patients. The number of total studies from the 3 groups exceeded 27 as several longitudinal studies reported depression in multiple treatment groups (i.e. in both pre-treatment and on-treatment groups).

Number of studies reporting anxiety

20 of the 26 studies entered into the review reported data on anxiety prevalence. Of these 20, 9 reported ~~depression~~ anxiety in pre-treatment patients, 4 in on-treatment patients and 11 in post-treatment patients.

Number of Patients Measured for Depression

Collectively, measures of depression were recorded from 5139 participants across the 26 studies. In terms of the individual treatment groups, 1259 participants provided measures of depression in the pre-treatment group, 723 in the on-treatment group and 3157 in the post treatment group.

Number of Patients Measured for Anxiety

Collectively, measures of anxiety were recorded from 4635 participants across the 20 studies. In terms of the individual treatment groups, 1057 participants provided measures of anxiety in the pre-treatment group, 501 in the on-treatment group and 3077 in the post treatment group.

Pre-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of depression was 17.27% (CI: 15.06%-19.72%).

Anxiety: Within the 9 studies that provided measures of anxiety in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of anxiety was 27.04% (CI: 24.26%-30.01%).

INSERT FIGURE 2

On-Treatment Depression and Anxiety Prevalence

Depression: Within the 9 studies that provided measures of depression in PCa patients currently undergoing treatment (see Figure 2), the prevalence of depression was 14.70% (CI: 11.92%-17.99%).

Anxiety: Within the 4 studies that provided measures of anxiety in PCa patients currently undergoing treatment (see Figure 2), the prevalence of anxiety was 15.09% (CI: 12.15%-18.60%).

INSERT FIGURE 3

Post-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients who had completed treatment (see Figure 3), the prevalence of depression was 18.44% (CI: 15.18%-22.22%).

Anxiety: Within the 11 studies that provided measures of anxiety in PCa patients who had completed treatment (see Figure 3), the prevalence of anxiety was 18.49% (CI: 13.81%-24.31%).

INSERT FIGURE 4

Depression and Anxiety Prevalence Across and Within Treatment Groups

Figure 4 provides a pictorial representation of the prevalence of depression and anxiety both within and across each of the three treatment groups.

INSERT FIGURE 5

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Discussion

There is a real need within clinical oncology, particularly as the burden of disease is escalating with improved diagnosis and treatment, for an increased awareness about the issue of psychological distress among men diagnosed with, being treated for and surviving through/living with a PCa diagnosis. The results of the current meta-analysis go some way in addressing this issue by providing those working within the field of PCa with a rigorous overview of the likely prevalence of depression and anxiety in the patients they treat. Our findings suggest that over the trajectory of the PCa journey, depression and anxiety prevalence are highest in patients who have yet to undergo treatment (17.27% and 27.4% respectively), lowest in patients who are currently undertaking treatment (14.70% and 15.90% respectively) before rising again in patients who have completed treatment (18.44% and 18.49% respectively). The relatively small variation observed within these prevalence rates across the different treatment stages, along with the large collective sample size of the

meta-analysis (4494) suggests these conclusions are valid powerful and robust summaries of the data available. The prevalence of clinical depression and anxiety in British men aged over 65 years is estimated to be less than 9% and 6%, respectively (~~35order of refs right~~ 35). Such data are in stark contrast to the prevalence reported in PCa patients of the same age in this study.

The current meta-analysis is the first of its kind to specifically assess the prevalence of clinical depression and anxiety in prostate cancer (PCa) patients over their treatment spectrum, from pre-treatment, through treatment to post-treatment follow up. To date, the lack of synthesis of the available data relating to depression and anxiety in PCa has meant that clinical decisions have been based on isolated research trials that lack sufficient power and depth in terms of sample sizes, treatment protocols and treatment stages. Consequently the true prevalence of psychological morbidity experienced by PCa patients across the treatment spectrum is poorly understood and described and this may result in patients being left untreated. We hope that with additional epidemiological investigation we will be able to offer a more risk adapted approach with more intensive screening and support being offered to individuals who are most at risk of psychological morbidity which may in part be related to their current stage of treatment. This is important as research suggests that cancer patients who are suffering from clinical depression and anxiety are less likely to adhere to their treatment plan and are more likely to experience adverse reactions to their treatment (4,5). Consequently, the identification, treatment and management concurrent psychological distress should be a key clinical objective as a means of enhancing both clinical outcomes and patient quality of life.

There are several limitations to the results generated by this review that need to be noted when interpreting the findings. There is a noticeable dearth of research into the prevalence of depression and anxiety in PCa patients with metastatic disease; we identified only 87 patients with metastatic PCa, out of the pooled sample size of 4494. Given the increased physical symptomology, and significantly lowered life expectancy, associated with metastatic PCa, it is possible that the prevalence of psychological morbidity within this patient cohort will probably be substantially higher. Unfortunately it was not possible to generate depression and anxiety prevalence data specifically for men with metastatic disease as the studies that recruited PCa patients with metastatic disease did so as part of larger collective samples of patients that included those with localised and/or advanced PCa. In the majority of cases, no individual depression and anxiety data was provided specifically for those with metastatic disease. Consequently it was not possible to describe these patients separately.

We do not know the overall proportion of men who suffer from some psychological distress during their PCa cancer journey from these largely cross-sectional studies. We suspect that

a number of individuals become depressed and anxious at various stages of their cancer journey and then may improve so overall the numbers of people affected at some stage may be higher than we are able to identify from this analysis. We would need to conduct a sustained longitudinal cohort study to resolve this question. Likewise, none of the included studies provided any form of data relating to the patients past history of depression and anxiety. Consequently it was not possible to determine whether a past history of depression and anxiety acted as a significant predictor of current depression and anxiety.

It is also important to note the wide variability in both the point prevalence estimates of anxiety and depression and the 95% confidence intervals associated with them. There are likely to be many reasons for this variability which include sample size, selective populations and the differing instruments that have been used to measure depression and anxiety. Unfortunately it was not possible to formally investigate the properties of the populations to determine whether there were any differences that would explain this variability. It is important that furture studies into the assessment of depression and anxiety in this patient group carefully identidy the characterisitcs of their populations to address this issue.

We were also not able to determine whether the prevalence of depression and anxiety was a factor influencing the type of PCa treatments provided to individuals. The associated side effects of PCa treatment include debilitating urinary, sexual and bowel dysfunction as well as the potentially negative psychological side effects of passive treatment options such as active surveillance (AS) and watchful waiting (WW), in which the patient faces living with a diagnosed but untreated cancer. This is an important clinical issue as it may provide a novel avenue in which to streamline the screening of depression and anxiety by offering patients undertaking treatments that have been shown to induce higher rates of distress with early, preventive support during their cancer journey.

Burnett et al (2007) reports that the prevalence of depression among AS/WW patients is just 4% (in a sample of 100 patients recruited from a single cancer centre of international excellence), leading the authors to conclude that AS does not predispose patients to higher levels of distress in comparison to those undergoing radical treatment. However our data identified that the prevalence of depression is almost three times higher than that reported by Burnett et al (2007) at 11% (within this specific population, suggesting that psychological distress may indeed be a substantial risk associated with AS/WW.

The utilisation and uptake of AS/WW within the UK is increasing (36), yet our results clearly highlight that the issue of psychological morbidity among these PCa patients is poorly described and defined, with only 4 of the 27 studies entered into this review obtaining measures of depression and anxiety from this patient population (22,23,27,34).

Consequently we suggest that patients being treated with AS/WW should be investigated in more detail to better understand the psychological ramifications of this form of management. Such research should ideally involve the recruitment of larger sample sizes (>200) from multiple sites to provide a more generalisable estimate of psychological distress from this patient cohort.

In conclusion, across the treatment spectrum, PCa patients appear to experience a moderate to high degree of psychological morbidity ranging from 15% to 27%. Most acute prevalences of depression and anxiety occur prior to and after the completion of treatment, the consequences of which may go on to negatively impact upon treatment compliance (6), increased periods of hospitalisation (5) and overall functional quality of life (37). Based on our findings we conclude that the assessment, diagnosis and treatment of depression and anxiety should be a key priority for any clinical oncology team working with PCa to enable them to optimise their patients' quality of life and clinical treatment outcomes.

Authors Contribution

Sam Watts: Protocol development, data searching, extraction and analysis and author

Dr Geraline Leydon: Co-author and academic supervisor

Mr Brian Birch: Co-author

Professor Philip Prescott: Statistical analysis

Mrs Lily Lia: Data extraction

Dr Susan Eardley: Data extraction

Professor George Lewith: Co-author and academic supervisor

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Tables

Table 1: Key features of the included studies

Author	Year	Location	Sample size	Participant Age	Cancer stage	Treatment stage
Ene	2006	Sweden.	123	63.1	No data provided	Pre to Post-treatment
Pirl	2008	USA.	50	62	Advanced	Pre and On-treatment
Sharpley	2007	Australia.	195	69.2	Localised	Post-treatment
Bisson	2002	Wales	83	64.5	Mixed	Pre-treatment
Dirkson	2009	USA	51	73.4	Mixed	On-treatment
Dale	2009	USA	67	67.9	No data provided	Pre-treatment (but all participants had received prior primary therapy)
Gabershagen	2007	Germany	115	64.1	Localised	Pre-treatment
Gabershagen	2009	Germany	84	62.8	Mixed	Pre-treatment to post-treatment
Hervouet	2005	Canada	861	67.9	Mixed	Post-treatment
Monga	1999	USA	36	66	Localised	Pre-treatment to On-treatment to Post treatment
Monga	2005	USA	40	67.8	Localised	Pre-treatment to On-treatment to Post-treatment
Pirl	2002	USA	45	69.4	Localised and Metastatic	On-treatment
Savard	2005	Canada	327	66	localised	Post-treatment
Stone	2000	England.	62	69	Mixed	On-treatment
Soloway	2004	USA	103	62	No data provided	Pre-treatment
Steineck	2002	Finland	326	64.5	Localised	Post-treatment
Symon	2006	USA	50	59.9	Localised	Pre-treatment to Post-treatment
Sharpley	2007	Australia.	183	69.2	Localised	Post-treatment
Sharpley	2009	Australia.	150	69.8	Localised	Post-treatment
van Tol-Geerdink	2006	Holland	118	70	Localised	Pre-treatment
Van den Berg	2009	Holland	129	64.9	Localised	On-treatment (active surveillance)
Van den Berg	2010	Holland	129	64.6	Localised	On-treatment (active surveillance)
Monga	2001	USA	40	67.6	Localised	Pre-treatment to Post-treatment
Korfage	2006	Holland	299	65.4	Mixed	Pre-Post treatment
Bitsika	2009	Australia	381	No data	Localised	Post-treatment
Nordin	2001	Sweden	118	No data	Localised & Advanced	Pre-treatment
Burnett	2007	England	329	68.8	Localised	On-treatment and post-treatment

Table 2: Overview of Study Characteristics

	All studies	Pre-Treatment Studies	On-Treatment Studies	Post-Treatment Studies
Study Samples (patient numbers)	4494	1707	723	3087
Participant Ages	66.3 (3.3)	64.8 (2.9)	67.6 (3.3)	66.9 (2.4)
Number of patients with localised PCa	3270	1299	563	2236
Number of patients with advanced PCa	513	162	72	441
Number of patients with metastatic PCa	87	58	40	7

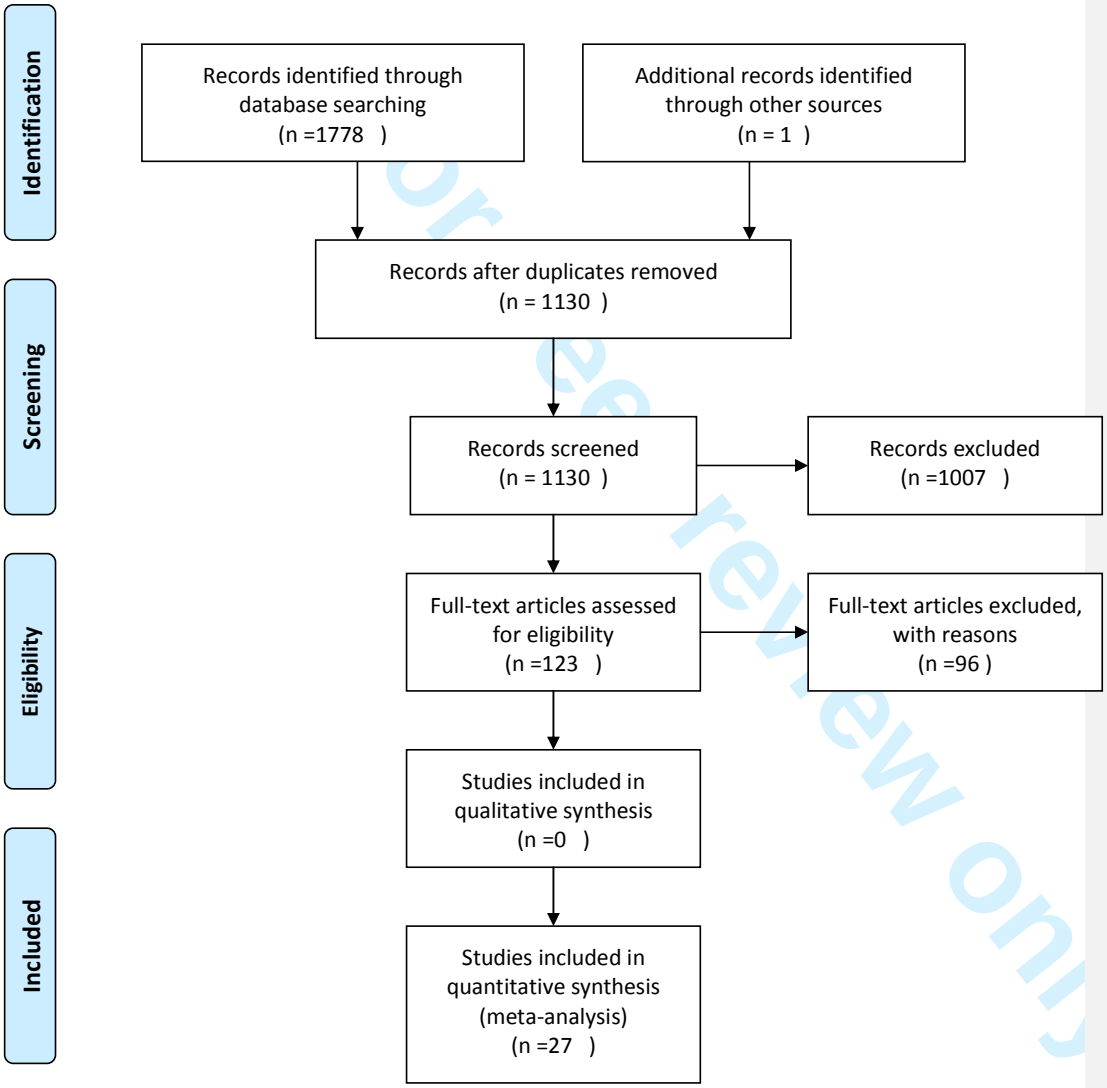
Table 3. The number of PCa patients being treated and undertaking each treatment modality

Radical Prostatectomy	Radiotherapy (EBRT & Brachytherapy)	Hormone Therapy (orchiectomy and ADT)	Chemotherapy	Active Surveillance or Watchful Waiting	Newly diagnosed (no treatment yet selected)
924	1578	264	24	418	304

Table 4. Questionnaires utilised , frequency of use and cut-off scores utilized

Questionnaire Name	Frequency of Use	Clinical Cut-Off Scores Utilised
Hospital Anxiety and Depression Scale (HADS)	13	HADS-A: ≥8 HADS-D: ≥8
Beck Depression Inventory (BDI)	6	≥10
Self Rating Anxiety Scale (SAS)	4	≥36
Self Rating Depression Scale (SDS)	4	≥40
Centre for Epidemiologic Studies Depression Scale (CES-D)	4	≥15
Stait-Trait Anxiety Scale (STAI)	4	≥44
Memorial Anxiety Scale for Prostate Cancer (MAX-PC)	3	≥27

Figure 1: PRISMA 2009 Flow Diagram



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
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	NA
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
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.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
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).	6
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.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
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.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
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.	7

PRISMA 2009 Checklist

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).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
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.	7
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.	8-9
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).	NA
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.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
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).	12
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).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
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.	3

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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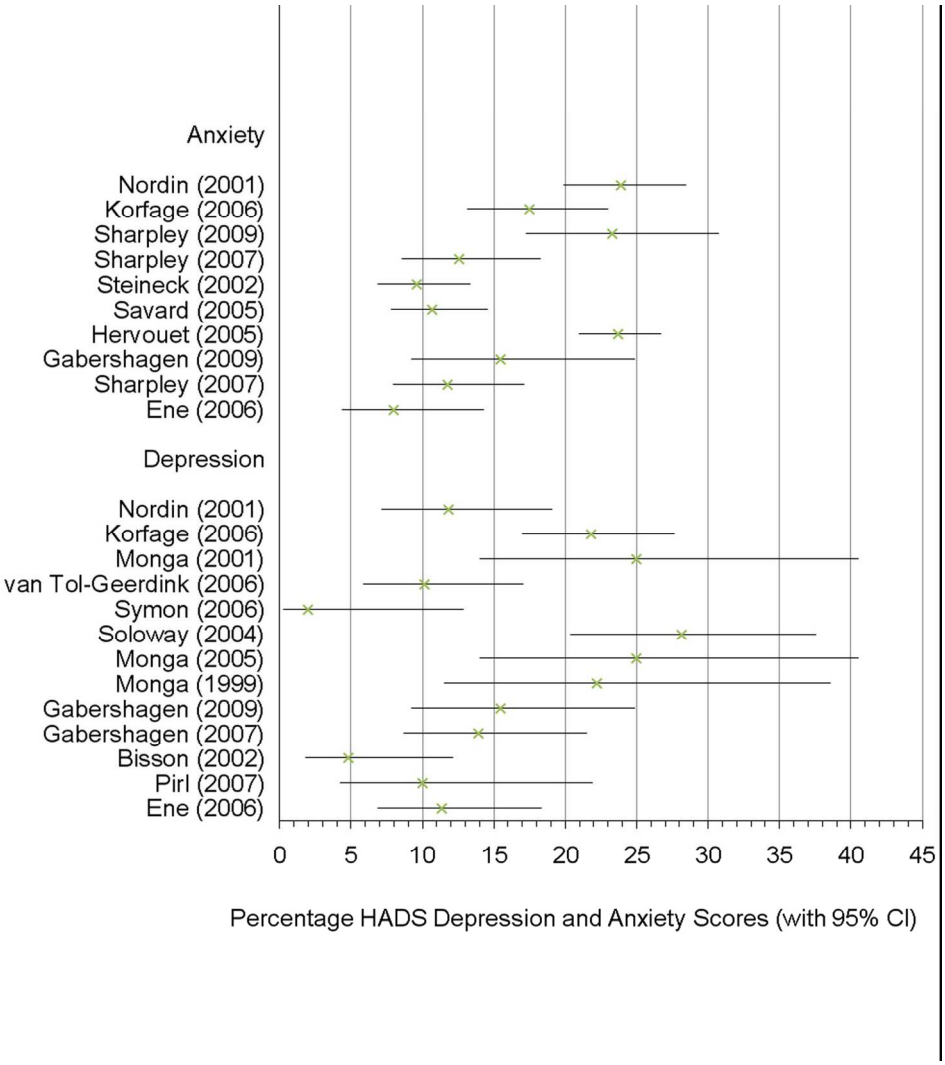

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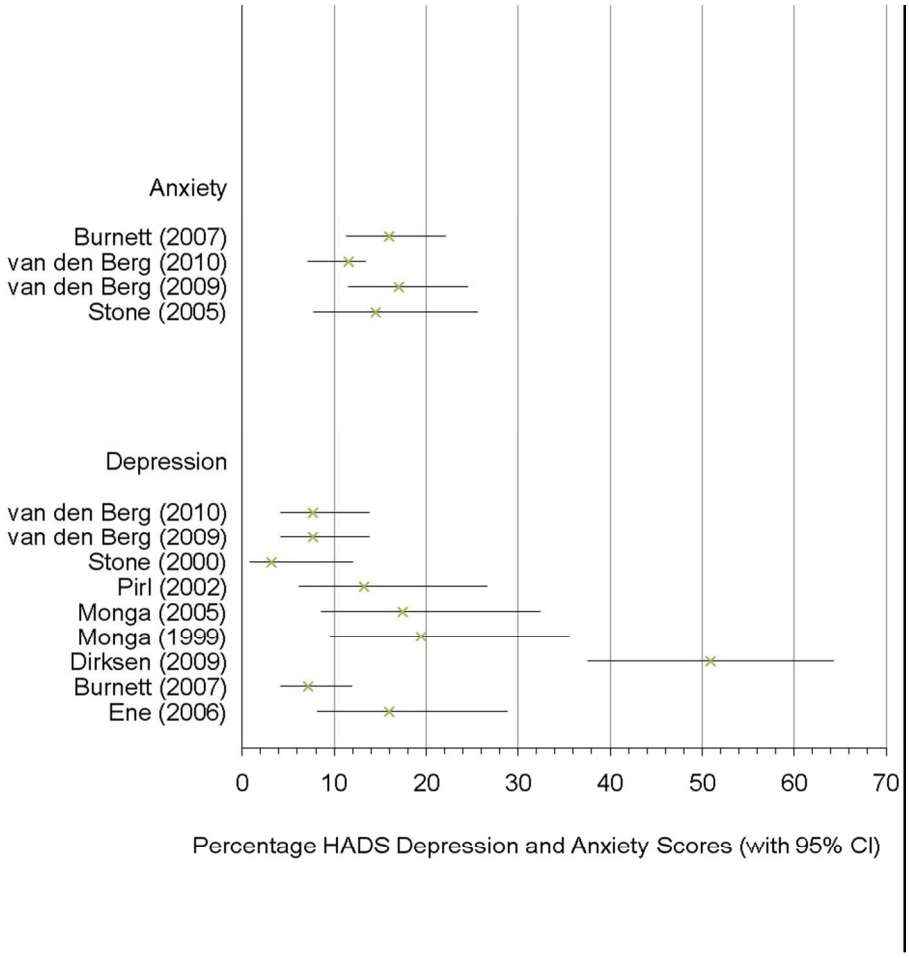

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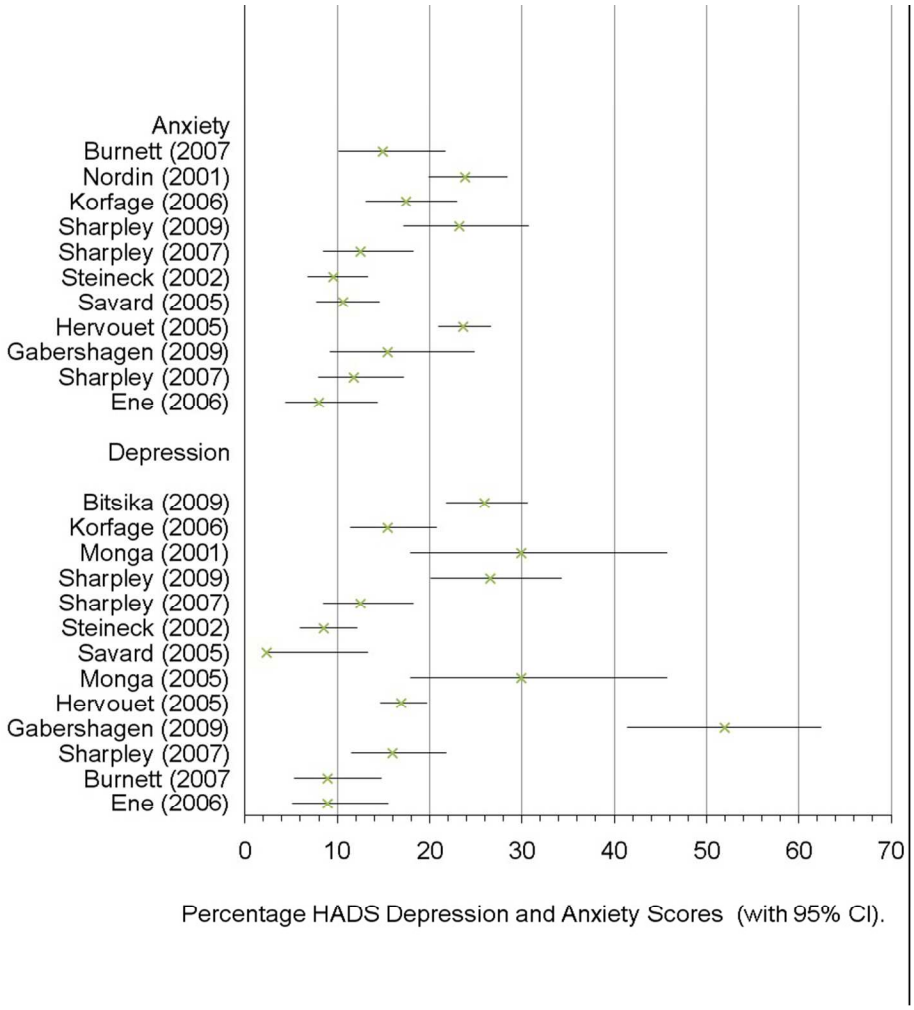

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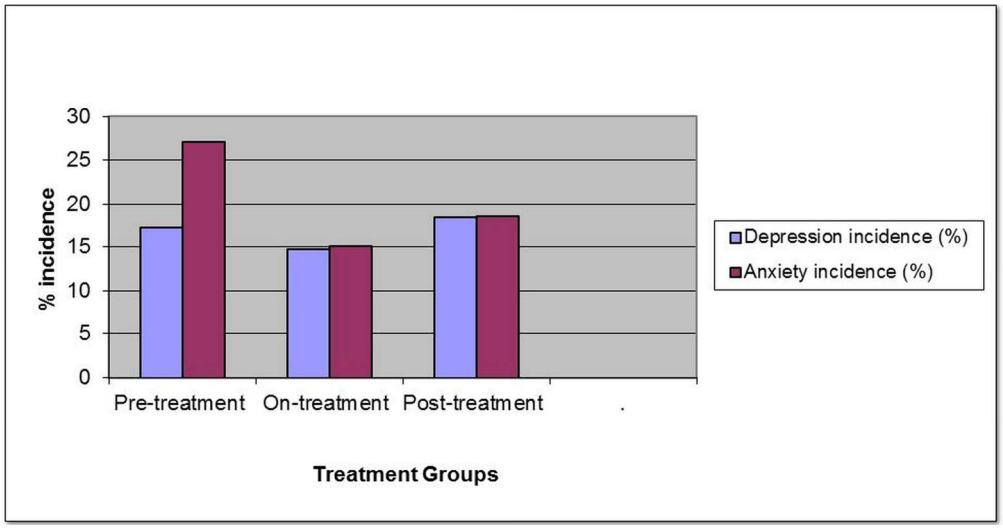

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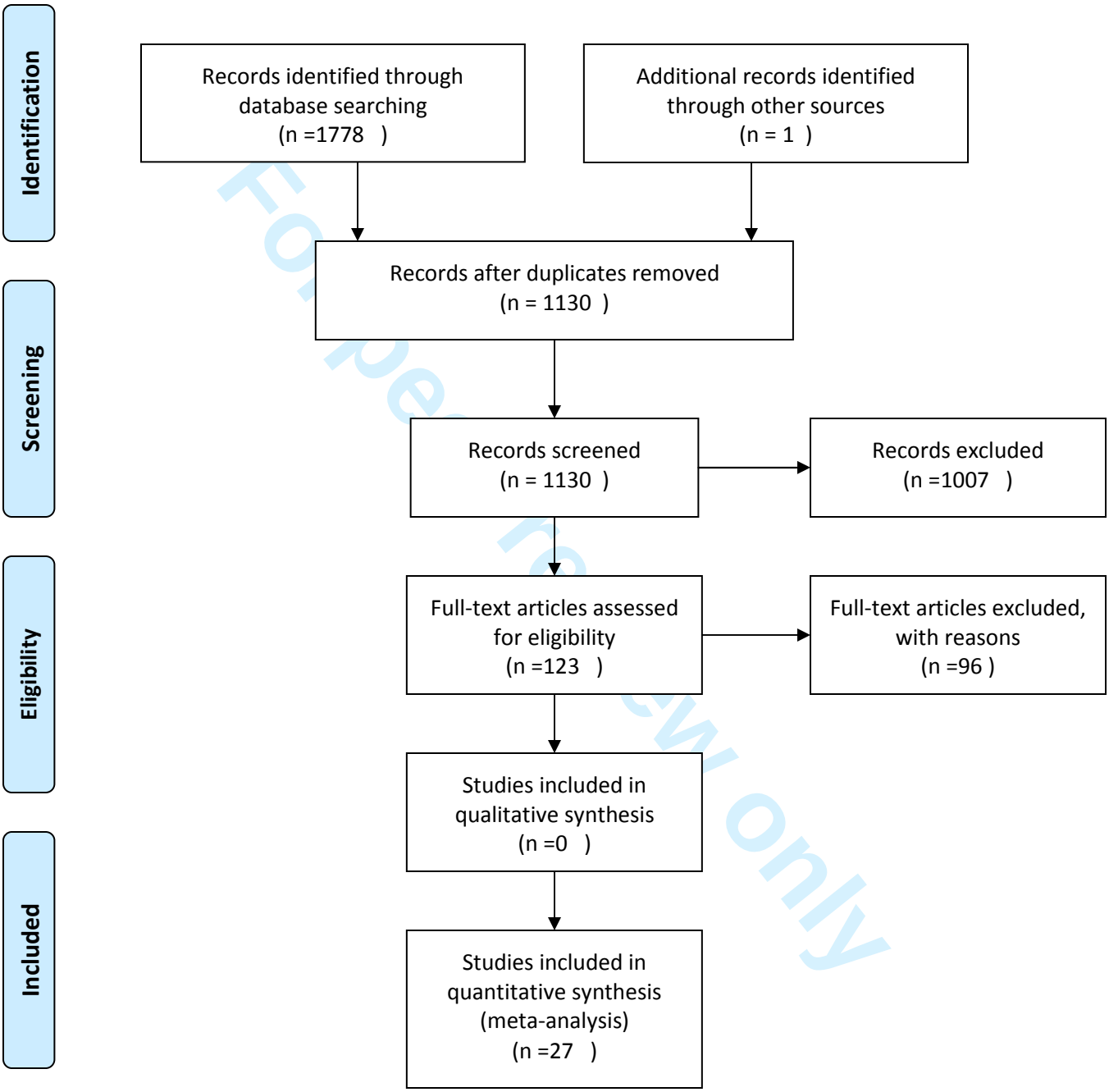
PRISMA 2009 Flow Diagram



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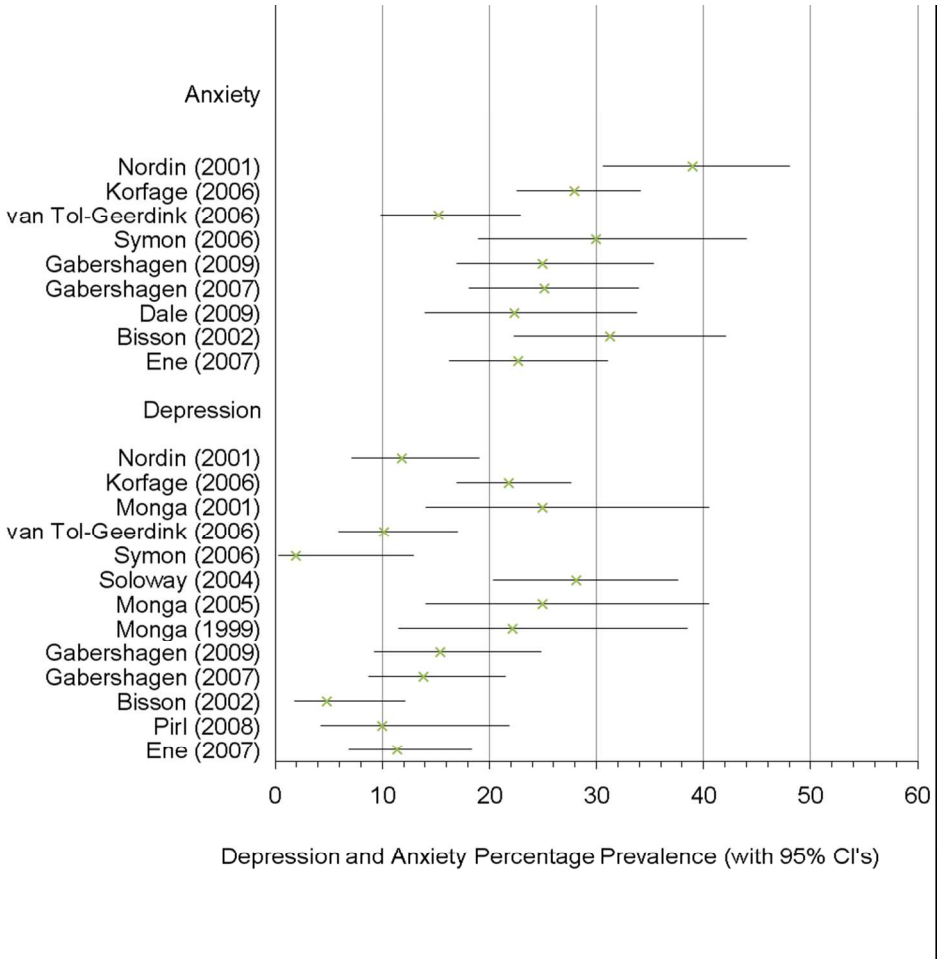

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Depression and Anxiety in Prostate Cancer: A Systematic Review and Meta-Analysis of Prevalence Rates

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Depression and Anxiety in Prostate Cancer: A Systematic Review and Meta-Analysis of Prevalence Rates

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Word Count: 3677

Abstract

Objectives: To systematically review the literature pertaining to the prevalence of depression and anxiety in prostate cancer patients as a function of treatment stage.

Design: Systematic review and meta-analysis

Participants: 4494 prostate cancer patients from primary research investigations.

Primary Outcome Measure: The prevalence of clinical depression and anxiety in prostate cancer patients as a function of treatment stage

Results: We identified 27 full journal articles that met the inclusion criteria for entry into the meta-analysis resulting in a pooled sample size of 4494 patients. The meta-analysis of prevalence rates identified pre-treatment, on-treatment and post-treatment depression prevalences of 17.27% (95% CI: 15.06%-19.72%), 14.70% (95% CI: 11.92%-17.99%) and 18.44% (95% CI: 15.18%-22.22%) respectively. Pre-treatment, on-treatment and post-treatment anxiety prevalences were 27.04% (95% CI: 24.26%-30.01%), 15.09% (95% CI: 12.15%-18.60%) and 18.49% (95% CI: 13.81%-24.31%) respectively.

Conclusions: Our findings suggest that the prevalence of depression and anxiety in men with prostate cancer, across the treatment spectrum, are relatively high. In light of the growing emphasis placed on cancer survivorship we consider that further research within this area is warranted to ensure psychological distress in prostate cancer patients is not under-diagnosed and under-treated.

Article Summary

Article Focus:

Identifying systematically how the prevalence of anxiety and depression in men with prostate cancer varies across the treatment trajectory, from pre-treatment to post-treatment follow up

Key Messages:

Prostate cancer patients display a significantly higher prevalence of depression and anxiety than the normal population across the treatment spectrum, particularly prior to and after the completion of treatment.

This has important implications for decision making, quality of life and survivorship in this population.

Further research is required to ensure that psychological distress in men with prostate cancer is clearly identified and managed appropriately

Strengths and Limitations:

This is the first meta-analysis to define depression and anxiety prevalence specifically within prostate cancer

Limited data is available for patients on active surveillance and with metastatic disease.

Cross-sectional methodologies make it difficult to draw definitive conclusions about the history and progression of anxiety and depression over the cancer journey in this population.

Introduction

Prostate cancer (PCa) represents the most common form of non-cutaneous malignancy diagnosed in British men (1). Over 36,000 new cases were diagnosed in 2007, accounting for almost 25% of the total yearly number of male cancer diagnoses (1). With an ageing UK population and increasing utilisation of PCa screening in asymptomatic men (2) the incidence rates of PCa are predicted to continue increasing year on year (1).

In light of such a substantial and sustained disease burden the management of survivorship issues within PCa becomes of paramount importance. Such issues revolve around the effective maintenance of quality of life (QoL) throughout the cancer journey, from initial diagnosis through to post-treatment survivorship. Additionally, the National Cancer Survivorship Initiative (NCSI) established five key goals of improved, personalized and patients centered care in the UK (3). One goal was the need to better address the specific psychological concerns associated with the diagnosis and treatment of cancer.

Depression and anxiety are two of the most commonly experienced psychological conditions experienced by cancer patients (4) and are associated with unique psycho-physiological side effects that importantly encompass poorer treatment outcomes (5), increased periods of hospitalisation (6) and higher mortality rates (7). With the advances in treatment efficacy, cancer is being increasingly viewed and treated as a chronic disease that can be effectively managed for many years. Given the longevity associated with the trajectory of PCa (over 70% of PCa patients can expect to live for ten years or more from the time of diagnosis) it is possible that the onset of psychological distress within this population of men is not an acute threat that quickly passes but a chronic one with peaks and troughs of severity that occur at key stages of the cancer journey.

The research base evaluating the prevalence of depression and anxiety within PCa is growing steadily and a sizeable body of clinically relevant research currently exists. Unfortunately much of this data is very heterogeneous and of poor methodological quality and has yet to be subjected to rigorous systematic review and meta-analysis. This lack of synthesis makes it very difficult for physicians and allied health care professionals working with PCa to access, interpret and apply the key research findings to their clinical practice.

It is as yet unclear what stages of the PCa cancer journey patients find most distressing. Were this known, or at least better understood, it would allow health care professionals to be more proactive and aware of what stages of treatment patients are most likely to experience depression and anxiety. This would allow health care teams to risk adapt their psychological screening and support processes.

The current meta-analysis was undertaken to address this issue and provide an initial baseline estimate of the prevalence of clinical depression and anxiety in PCa patients during each of the three key stages of cancer treatment; pre-treatment, on-treatment and post-treatment.

Method

Eligibility Criteria

Studies that investigated the specific prevalence of depression and anxiety in prostate cancer (PCa) patients in full journal articles were included. Studies published in conference proceedings, qualitative research, commentaries and discussions, letters, books, book chapters or research not published in the English language were excluded.

Eligible studies were restricted to research focusing on individuals with a biopsy confirmed diagnosis of PCa. If PCa patients were included within an investigation that recruited mixed cancer populations, the study was required to have reported data about the PCa patients as a distinct sub-sample. The primary outcome for the current meta-analysis was the prevalence of depression and anxiety. Thus inclusion into the meta-analysis was restricted to those studies that reported PCa specific prevalence data for depression and anxiety separately.

To be eligible for inclusion, each study was required to provide a clear definition of the PCa treatments undertaken by the study participants and when such treatments took place (i.e. treatment that was yet to be undertaken, was being undertaken at the time of the study or had already been completed. For the latter category, it was a requirement that the authors specified the time lapse since the cessation of treatment).

Questionnaire Analysis

Entry into the meta-analysis was also restricted to data that were collected from questionnaires that provided specific, valid and reliable measurements of depression and anxiety. To enable this, a series of questionnaire specific inclusion criteria were created against which all of the questionnaires utilised in the studies could be assessed; each questionnaire must:

Allow for the specific and independent measurement of depression and anxiety.

Have available established threshold information (measurements) for the diagnosis of depression and anxiety.

The validity of each questionnaire must have been assessed in comparison to established “gold standard” questionnaires.

The internal validity and reliability of each questionnaire must have been assessed and deemed acceptable (test-retest).

Twelve questionnaires meeting the criteria were identified which included the Hospital Anxiety and Depression Scale, Stait -Trait Anxiety Scale, Centre for Epidemiologic Studies Depression Scale, Symptom Checklist, Beck Depression Inventory, Self-Rating Anxiety Scale, Self-Rating Depression Scale, Brief Symptom Inventory, Composite International Diagnostic Interview, Memorial Anxiety Scale for Prostate Cancer and the Effects of Prostate Cancer on Lifestyle Questionnaire

Identifying Research Evidence

Data searches were conducted between June 2011 and August 2011. The search protocol was subsequently re-run in June 2013 to ensure no additional data were identified. We searched 6 electronic databases (OVID Medline, EMBASE, AMED, PsycINFO, CINAHL and Web of Science) for articles that met the previously discussed criteria using pre-specified MESH terms as that included Prostate Neoplasm (EXP)” OR “Prostate Cancer” AND “Depression (EXP)” or “Anxiety (EXP)” or “Psychological distress (EXP” or “Stress (EXP)” or “Distress (EXP)”. No restrictions on publication dates were imposed.

To supplement the electronic searches we also conducted searches of the reference lists of previous reviews, key papers and other relevant articles identified by the electronic search. We also conducted systematic searches of the content lists of key journals to identify any additional studies missed by the electronic search.

Study Selection

Titles and abstracts were initially assessed for eligibility. If it was possible to confirm that an article met the inclusion criteria from the abstract alone, the full text article was retrieved. If it was clear from the abstract that an article was not eligible, it was rejected immediately. If it was not possible to determine the eligibility of an article from the abstract, the full text article was retrieved. If any key information was missing, we contacted the authors for the missing data. If this was not possible or ineffective, the study was rejected, (see Figure 1).

Data Extraction

The following specific information relating to data collection and results was extracted individually from each identified article and entered into a pre-designed Excel spread sheet: date and geographical location of data collection; aims and objectives of the investigation; study design; participant inclusion and exclusion criteria; recruitment procedures; sample size; disease stage; socio-demographic status (age, ethnicity and relationship, educational and employment status); time since diagnosis; additional co-morbidity; stage of treatment (pre, on or post-treatment); treatments undertaken (surgery, radiotherapy, hormone therapy, chemotherapy, active-surveillance/watchful waiting); questionnaires utilised; statistical analyses performed; depression prevalence (%) and anxiety prevalence (%).

To test the consistency of data extraction across the studies, three researchers (SW, LL, SE) extracted data from the same 6 randomly selected articles then compared the results of their extraction. A points system was utilised to allow for the objective assessment of consistency. 1 point was allocated for variables with identical data extraction and 0 points for variables with differences. Across all ratings, consistency ranged from 92% to 96% (median: 94%).

Meta-Analysis Procedure

Given the range of estimated proportions expected within the extracted data, the logits of proportions method of conducting the statistical analysis was employed, rather than utilising normal approximations of binomial distributions.

Cochran's Q test was applied to the logits to test the hypothesis of homogeneity of the within study estimates of the proportions, with larger Q values suggesting that the estimates are not homogeneous. Initial analyses highlighted Q values between Q= 15.2 and 215, with some of the larger values suggesting a degree of heterogeneity, the result in some cases of only one or two studies being out of line with the others. For completeness, meta-analysis results have been provided even for those cases where heterogeneity is evident.

Results

Search Results

The electronic database searches initially yielded 1778 journal article references. 1655 of these were subsequently removed due to either duplication or a failure to meet the inclusion criteria. Full text articles were then retrieved and critically appraised for the remaining 123 journal references. Of these 123 articles 97 did not meeting the inclusion criteria. The remaining 26 articles were entered into the meta-analysis.

Hand searches of the key journals identified by the electronic database search revealed no additional journal articles. Searching the reference lists of articles identified through the electronic database search identified 2 journal article references of interest that had otherwise been missed. Full text articles were retrieved for these 2 references, one of which could be included making the total included 27. (Figure 1).

INSERT FIGURE 1

Study Locations

Of the 27 studies entered into the review, 9 were conducted within America (6,8,9,10, 11,12,13,14,15), 4 in both Australia (16,17,18,19) and Holland (20,21,22,23), 3 in the UK (24,25,26), 2 each in Sweden (27,28), Germany (29,30) and Canada (31,32) and 1 in Finland (33). An overview of the key features of each of the included studies can be seen in Table 1.

INSERT TABLE 1

Study Sample Sizes

The samples sizes of the studies entered into the review varied widely from 36 to 861. The total sample size across all 27 studies was 4494 with a mean sample size of 158. The sample sizes of the individual treatment stage groups (pre, on and post-treatment) can be seen in Table 2.

Participant Age

Data on participant age was reported by 24 of the 27 studies and in all 24 cases mean age was reported. The range of mean ages across the 24 studies varied from 57.5 years to 73.2 years. The mean age of all participants across the 24 studies was 66.3 years (3.3). Three

studies failed to report participant age in any format. The mean age of the participants in each of the three treatment groups can be seen in Table 2.

Cancer Staging

Data regarding participant cancer stage was reported by 23 of the 27 studies. There was a general lack of consistency regarding reporting methods. Several studies utilised the clinical T-staging system of T1 (localised) to T4 (metastatic) whilst the majority simply graded PCa as localised, advanced or metastatic. No study reported patient disease stage using the recommended tumour-nodes-metastasis (TNM). The majority of patients had been diagnosed with localised disease (n=3270), followed by advanced (513) and metastatic PCa (87), as shown in Table 2.

INSERT TABLE 2

Cancer Treatments Undertaken

Table 3 provides an overview of the number of participants undergoing each PCa treatment. Unfortunately, it was not possible to stratify the treatments undertaken as a function of either disease stage (localised, advanced or metastatic) or treatment stage (on-treatment or post-treatment). This was because in many instances patients with different disease staging or who were at different treatment stages were recruited into the same cohort. Consequently, whilst the number of patients completing each type of treatment was clearly highlighted, it was not possible to determine whether the patients with localized, advanced or metastatic disease, nor those who were either on or post-treatment, had completed them. Thus the data in Table 3 provides a collective overview of the treatments undertaken by all of the patients, irrespective of disease or treatment stage. Additionally, several of the pre-treatment studies recruited participants who had yet to decide upon treatment. Such patients are listed in Table 3 as 'newly diagnosed'.

INSERT TABLE 3

2.6. Questionnaires Analysis

Of the 12 questionnaires meeting the questionnaire inclusion criteria as listed in the method section, only 7 were utilised by the 27 studies entered into this meta-analysis. Table 4 lists the 7 questionnaires, the frequency with which they were used and the clinical cut-off scores utilized to determine caseness.

INSERT TABLE 4

Meta-Analysis of Depression and Anxiety Prevalence

Number of studies reporting depression

26 of the 27 studies entered into the review reported data on depression prevalence. Of these 26, 13 reported depression in pre-treatment patients, 9 in on-treatment patients, and 13 in post-treatment patients. The number of total studies from the 3 groups exceeded 27 as several longitudinal studies reported depression in multiple treatment groups (i.e. in both pre-treatment and on-treatment groups).

Number of studies reporting anxiety

20 of the 26 studies entered into the review reported data on anxiety prevalence. Of these 20, 9 reported anxiety in pre-treatment patients, 4 in on-treatment patients and 11 in post-treatment patients.

Number of Patients Measured for Depression

Collectively, measures of depression were recorded from 5139 participants across the 26 studies. In terms of the individual treatment groups, 1259 participants provided measures of depression in the pre-treatment group, 723 in the on-treatment group and 3157 in the post treatment group.

Number of Patients Measured for Anxiety

Collectively, measures of anxiety were recorded from 4635 participants across the 20 studies. In terms of the individual treatment groups, 1057 participants provided measures of

anxiety in the pre-treatment group, 501 in the on-treatment group and 3077 in the post treatment group.

Pre-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of depression was 17.27% (CI: 15.06%-19.72%).

Anxiety: Within the 9 studies that provided measures of anxiety in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of anxiety was 27.04% (CI: 24.26%-30.01%).

INSERT FIGURE 2

On-Treatment Depression and Anxiety Prevalence

Depression: Within the 9 studies that provided measures of depression in PCa patients currently undergoing treatment (see Figure 2), the prevalence of depression was 14.70% (CI: 11.92%-17.99%).

Anxiety: Within the 4 studies that provided measures of anxiety in PCa patients currently undergoing treatment (see Figure 2), the prevalence of anxiety was 15.09% (CI: 12.15%-18.60%).

INSERT FIGURE 3

Post-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients who had completed treatment (see Figure 3), the prevalence of depression was 18.44% (CI: 15.18%-22.22%).

Anxiety: Within the 11 studies that provided measures of anxiety in PCa patients who had completed treatment (see Figure 3), the prevalence of anxiety was 18.49% (CI: 13.81%-24.31%).

INSERT FIGURE 4

Depression and Anxiety Prevalence Across and Within Treatment Groups

Figure 4 provides a pictorial representation of the prevalence of depression and anxiety both within and across each of the three treatment groups.

INSERT FIGURE 5

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Discussion

There is a real need within clinical oncology, particularly as the burden of disease is escalating with improved diagnosis and treatment, for an increased awareness about the issue of psychological distress among men diagnosed with, being treated for and surviving through/living with a PCa diagnosis. The results of the current meta-analysis go some way in addressing this issue by providing those working within the field of PCa with a rigorous overview of the likely prevalence of depression and anxiety in the patients they treat.

Our findings suggest that over the trajectory of the PCa journey, depression and anxiety prevalence are highest in patients who have yet to undergo treatment (17.27% and 27.4% respectively), lowest in patients who are currently undertaking treatment (14.70% and 15.90% respectively) before rising again in patients who have completed treatment (18.44% and 18.49% respectively). The relatively small variation observed within these prevalence rates across the different treatment stages, along with the large collective sample size of the meta-analysis (4494) suggests these conclusions are valid, powerful and robust summaries

of the data available. The prevalence of clinical depression and anxiety in British men aged over 65 years is estimated to be less than 9% and 6%, respectively (34). Such data are in stark contrast to the prevalence reported in PCa patients of the same age in this study.

The current meta-analysis is the first of its kind to specifically assess the prevalence of clinical depression and anxiety in prostate cancer (PCa) patients over their treatment spectrum, from pre-treatment, through treatment to post-treatment follow up. To date, the lack of synthesis of the available data relating to depression and anxiety in PCa has meant that clinical decisions have been based on isolated research trials that lack sufficient power and depth in terms of sample sizes, treatment protocols and treatment stages. Consequently the true prevalence of psychological morbidity experienced by PCa patients across the treatment spectrum is poorly understood and described and this may result in patients being left untreated.

We hope that with additional epidemiological investigation we will be able to offer a more risk adapted approach with more intensive screening and support being offered to individuals who are most at risk of psychological morbidity which may in part be related to their current stage of treatment. This is important as research suggests that cancer patients who are suffering from clinical depression and anxiety are less likely to adhere to their treatment plan and are more likely to experience adverse reactions to their treatment (4,5). Indeed, recently published research has specifically highlighted the negative impacts of PCa specific anxiety on post-treatment survivorship in the form of poorer sexual function and increased depressive symptomology, further supporting the need for effective and timely intervention (35).

Consequently, the identification, treatment and management of concurrent psychological distress should be a key clinical objective as a means of enhancing both clinical outcomes and patient quality of life. Identifying which stage of treatment PCa patients are most likely to experience such conditions is an important first step to achieving this.

There are several limitations to the results generated by this review that need to be noted when interpreting the findings. There is a noticeable dearth of research into the prevalence of depression and anxiety in PCa patients with metastatic disease; we identified only 87 patients with metastatic PCa, out of the pooled sample size of 4494. Given the increased physical symptomology, and significantly lowered life expectancy, associated with metastatic PCa, it is possible that the prevalence of psychological morbidity within this patient cohort will probably be substantially higher. Unfortunately it was not possible to generate depression and anxiety prevalence data specifically for men with metastatic disease as the studies that recruited PCa patients with metastatic disease did so as part of larger collective

samples of patients that included those with localized and/or advanced PCa. In the majority of cases, no individual depression and anxiety data were provided specifically for those with metastatic disease. Consequently it was not possible to describe these patients separately.

We do not know the overall proportion of men who suffer from some psychological distress during their PCa cancer journey from these largely cross-sectional studies. We suspect that a number of individuals become depressed and anxious at various stages of their cancer journey and then may improve so overall the numbers of people affected at some stage may be higher than we are able to identify from this analysis. We would need to conduct a sustained longitudinal cohort study to resolve this question. Likewise, none of the included studies provided any form of data relating to the patients past history of depression and anxiety. Consequently it was not possible to determine whether a past history of depression and anxiety acted as a significant predictor of current depression and anxiety.

Furthermore this study did not compare the depression and anxiety prevalence rates generated directly to that observed in a cohort to healthy men or men with other cancers. As a consequence we were unable to specifically determine how PCa and its treatment impacted upon the prevalence of psychological distress observed. The essentially descriptive nature of this study therefore needs to be noted.

It is also important to note the wide variability in both the point prevalence estimates of anxiety and depression and the 95% confidence intervals associated with them. There are likely to be many reasons for this variability which include sample size, the differing instruments that have been used to measure depression and anxiety, selective populations and post-treatment outcomes. For example, it is possible that depression and anxiety prevalence in post-prostatectomy patients would vary substantially depending upon factors such as positive or negative margin status. Unfortunately it was not possible to formally investigate the properties of the populations to determine whether there were any such differences that would explain this variability. This represents an important limitation to the findings of this study. It is important that future studies into the assessment of depression and anxiety in this patient group carefully identify the characteristics of their populations to address this issue.

We were also not able to determine whether the prevalence of depression and anxiety was a factor influencing the type of PCa treatments provided to individuals. The associated side effects of PCa treatment include debilitating urinary, sexual and bowel dysfunction as well as the potentially negative psychological side effects of passive treatment options such as active surveillance (AS) and watchful waiting (WW), in which the patient faces living with a diagnosed but untreated cancer. This is an important clinical issue as it may provide a novel

avenue in which to streamline the screening of depression and anxiety by offering patients undertaking treatments that have been shown to induce higher rates of distress with early, preventive support during their cancer journey.

Burnett et al (2007) reports that the prevalence of depression among AS/WW patients is just 4% (in a sample of 100 patients recruited from a single cancer centre of international excellence), leading the authors to conclude that AS does not predispose patients to higher levels of distress in comparison to those undergoing radical treatment. However our data identified that the prevalence of depression is almost three times higher than that reported by Burnett et al (2007) at 11% (within this specific population, suggesting that psychological distress may indeed be a substantial risk associated with AS/WW.

The utilisation and uptake of AS/WW within the UK is increasing (36), yet our results clearly highlight that the issue of psychological morbidity among these PCa patients is poorly described and defined, with only 4 of the 27 studies entered into this review obtaining measures of depression and anxiety from this patient population (21,22,26,33). Consequently we suggest that patients being treated with AS/WW should be investigated in more detail to better understand the psychological ramifications of this form of management. Such research should ideally involve the recruitment of larger sample sizes (>200) from multiple sites to provide a more generalisable estimate of psychological distress from this patient cohort.

In conclusion, across the treatment spectrum, PCa patients appear to experience a moderate to high degree of psychological morbidity ranging from 15% to 27%. Most acute prevalences of depression and anxiety occur prior to and after the completion of treatment, the consequences of which may go on to negatively impact upon treatment compliance (6), increased periods of hospitalisation (5) and overall functional quality of life (37). Based on our findings we conclude that the assessment, diagnosis and treatment of depression and anxiety should be a key priority for any clinical oncology team working with PCa to enable them to optimise their patients' quality of life and clinical treatment outcomes.

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Authors Contribution

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Tables

Table 1: Key features of the included studies

Author	Year	Location	Sample size	Participant Age	Cancer stage	Treatment stage
Ene	2006	Sweden.	123	63.1	No data provided	Pre to Post-treatment
Pirl	2008	USA.	50	62	Advanced	Pre and On-treatment
Sharpley	2007	Australia.	195	69.2	Localised	Post-treatment
Bisson	2002	Wales	83	64.5	Mixed	Pre-treatment
Dirkson	2009	USA	51	73.4	Mixed	On-treatment
Dale	2009	USA	67	67.9	No data provided	Pre-treatment (but all participants had received prior primary therapy)
Gabershagen	2007	Germany	115	64.1	Localised	Pre-treatment
Gabershagen	2009	Germany	84	62.8	Mixed	Pre-treatment to post-treatment
Hervouet	2005	Canada	861	67.9	Mixed	Post-treatment
Monga	1999	USA	36	66	Localised	Pre-treatment to On-treatment to Post treatment
Monga	2005	USA	40	67.8	Localised	Pre-treatment to On-treatment to Post-treatment
Pirl	2002	USA	45	69.4	Localised and Metastatic	On-treatment
Savard	2005	Canada	327	66	localised	Post-treatment
Stone	2000	England.	62	69	Mixed	On-treatment
Soloway	2004	USA	103	62	No data provided	Pre-treatment
Steineck	2002	Finland	326	64.5	Localised	Post-treatment
Symon	2006	USA	50	59.9	Localised	Pre-treatment to Post-treatment
Sharpley	2007	Australia.	183	69.2	Localised	Post-treatment
Sharpley	2009	Australia.	150	69.8	Localised	Post-treatment
van Tol-Geerdink	2006	Holland	118	70	Localised	Pre-treatment
Van den Berg	2009	Holland	129	64.9	Localised	On-treatment (active surveillance)
Van den Berg	2010	Holland	129	64.6	Localised	On-treatment (active surveillance)
Monga	2001	USA	40	67.6	Localised	Pre-treatment to Post-treatment
Korfage	2006	Holland	299	65.4	Mixed	Pre-Post treatment
Bitsika	2009	Australia	381	No data	Localised	Post-treatment
Nordin	2001	Sweden	118	No data	Localised & Advanced	Pre-treatment
Burnet	2007	England	329	68.8	Localised	On-treatment and post-treatment

Table 2: Overview of Study Characteristics

	All studies	Pre-Treatment Studies	On-Treatment Studies	Post-Treatment Studies
Study Samples (patient numbers)	4494	1707	723	3087
Participant Ages	66.3 (3.3)	64.8 (2.9)	67.6 (3.3)	66.9 (2.4)
Number of patients with localised PCa	3270	1299	563	2236
Number of patients with advanced PCa	513	162	72	441
Number of patients with metastatic PCa	87	58	40	7

Table 3. The number of PCa patients being treated and undertaking each treatment modality

Radical Prostatectomy	Radiotherapy (EBRT & Brachytherapy)	Hormone Therapy (orchiectomy and ADT)	Chemotherapy	Active Surveillance or Watchful Waiting	Newly diagnosed (no treatment yet selected)
924	1578	264	24	418	304

Table 4. Questionnaires utilised , frequency of use and cut-off scores utilized

Questionnaire Name	Frequency of Use	Clinical Cut-Off Scores Utilised
Hospital Anxiety and Depression Scale (HADS)	13	HADS-A: ≥8 HADS-D: ≥8
Beck Depression Inventory (BDI)	6	≥10
Self Rating Anxiety Scale (SAS)	4	≥36
Self Rating Depression Scale (SDS)	4	≥40
Centre for Epidemiologic Studies Depression Scale (CES-D)	4	≥15
Stait-Trait Anxiety Scale (STAI)	4	≥44
Memorial Anxiety Scale for Prostate Cancer (MAX-PC)	3	≥27

Depression and Anxiety in Prostate Cancer: A Systematic Review and Meta-Analysis of Prevalence Rates

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Abstract

Objectives: To systematically review the literature pertaining to the prevalence of depression and anxiety in prostate cancer patients as a function of treatment stage.

Design: Systematic review and meta-analysis

Participants: 4494 prostate cancer patients from primary research investigations.

Primary Outcome Measure: The prevalence of clinical depression and anxiety in prostate cancer patients as a function of treatment stage

Results: We identified 27 full journal articles that met the inclusion criteria for entry into the meta-analysis resulting in a pooled sample size of 4494 patients. The meta-analysis of prevalence rates identified pre-treatment, on-treatment and post-treatment depression prevalences of 17.27% (95% CI: 15.06%-19.72%), 14.70% (95% CI: 11.92%-17.99%) and 18.44% (95% CI: 15.18%-22.22%) respectively. Pre-treatment, on-treatment and post-treatment anxiety prevalences were 27.04% (95% CI: 24.26%-30.01%), 15.09% (95% CI: 12.15%-18.60%) and 18.49% (95% CI: 13.81%-24.31%) respectively.

Conclusions: Our findings suggest that the prevalence of depression and anxiety in men with prostate cancer, across the treatment spectrum, are relatively high. In light of the growing emphasis placed on cancer survivorship we consider that further research within this area is warranted to ensure psychological distress in prostate cancer patients is not under-diagnosed and under-treated.

Article Summary

Article Focus:

Identifying systematically how the prevalence of anxiety and depression in men with prostate cancer varies across the treatment trajectory, from pre-treatment to post-treatment follow up

Key Messages:

Prostate cancer patients display a significantly higher prevalence of depression and anxiety than the normal population across the treatment spectrum, particularly prior to and after the completion of treatment.

This has important implications for decision making, quality of life and survivorship in this population.

Further research is required to ensure that psychological distress in men with prostate cancer is clearly identified and managed appropriately

Strengths and Limitations:

This is the first meta-analysis to define depression and anxiety prevalence specifically within prostate cancer

Limited data is available for patients on active surveillance and with metastatic disease.

Cross-sectional methodologies make it difficult to draw definitive conclusions about the history and progression of anxiety and depression over the cancer journey in this population.

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Competing Interests: None declared.

Introduction

Prostate cancer (PCa) represents the most common form of non-cutaneous malignancy diagnosed in British men (1). Over 36,000 new cases were diagnosed in 2007, accounting for almost 25% of the total yearly number of male cancer diagnoses (1). With an ageing UK population and increasing utilisation of PCa screening in asymptomatic men (2) the incidence rates of PCa are predicted to continue increasing year on year (1).

In light of such a substantial and sustained disease burden the management of survivorship issues within PCa becomes of paramount importance. Such issues revolve around the effective maintenance of quality of life (QoL) throughout the cancer journey, from initial diagnosis through to post-treatment survivorship. Additionally, the National Cancer Survivorship Initiative (NCSI) established five key goals of improved, personalized and patients centered care in the UK (3). One goal was the need to better address the specific psychological concerns associated with the diagnosis and treatment of cancer.

Depression and anxiety are two of the most commonly experienced psychological conditions experienced by cancer patients (4) and are associated with unique psycho-physiological side effects that importantly encompass poorer treatment outcomes (5), increased periods of hospitalisation (6) and higher mortality rates (7). With the advances in treatment efficacy, cancer is being increasingly viewed and treated as a chronic disease that can be effectively managed for many years. Given the longevity associated with the trajectory of PCa (over 70% of PCa patients can expect to live for ten years or more from the time of diagnosis) it is possible that the onset of psychological distress within this population of men is not an acute threat that quickly passes but a chronic one with peaks and troughs of severity that occur at key stages of the cancer journey.

The research base evaluating the prevalence of depression and anxiety within PCa is growing steadily and a sizeable body of clinically relevant research currently exists. Unfortunately much of this data is very heterogeneous and of poor methodological quality and has yet to be subjected to rigorous systematic review and meta-analysis. This lack of synthesis makes it very difficult for physicians and allied health care professionals working with PCa to access, interpret and apply the key research findings to their clinical practice.

It is as yet unclear what stages of the PCa cancer journey patients find most distressing. Were this known, or at least better understood, it would allow health care professionals to be more proactive and aware of what stages of treatment patients are most likely to experience depression and anxiety. This would allow health care teams to risk adapt their psychological screening and support processes.

The current meta-analysis was undertaken to address this issue and provide an initial baseline estimate of the prevalence ~~incidence~~ of clinical depression and anxiety in PCa patients during each of the three key stages of cancer treatment; pre-treatment, on-treatment and post-treatment.

Method

Eligibility Criteria

Studies that investigated the specific prevalence of depression and anxiety in prostate cancer (PCa) patients in full journal articles were included. Studies published in conference proceedings, qualitative research, commentaries and discussions, letters, books, book chapters or research not published in the English language were excluded.

Eligible studies were restricted to research focusing on individuals with a biopsy confirmed diagnosis of PCa. If PCa patients were included within an investigation that recruited mixed cancer populations, the study was required to have reported data about the PCa patients as a distinct sub-sample. The primary outcome for the current meta-analysis was the prevalence of depression and anxiety. Thus inclusion into the meta-analysis was restricted to those studies that reported PCa specific prevalence data for depression and anxiety separately.

To be eligible for inclusion, each study was required to provide a clear definition of the PCa treatments undertaken by the study participants and when such treatments took place (i.e. treatment that was yet to be undertaken, was being undertaken at the time of the study or had already been completed. For the latter category, it was a requirement that the authors specified the time lapse since the cessation of treatment).

Questionnaire Analysis

Entry into the meta-analysis was also restricted to data that ~~was~~ were collected from questionnaires that provided specific, valid and reliable measurements of depression and anxiety. To enable this, a series of questionnaire specific inclusion criteria were created against which all of the questionnaires utilised in the studies could be assessed; each questionnaire must:

Allow for the specific and independent measurement of depression and anxiety.

Have available established threshold information (measurements) for the diagnosis of depression and anxiety.

The validity of each questionnaire must have been assessed in comparison to established “gold standard” questionnaires.

The internal validity and reliability of each questionnaire must have been assessed and deemed acceptable (test-retest).

Twelve questionnaires meeting the criteria were identified which included the Hospital Anxiety and Depression Scale, Stait -Trait Anxiety Scale, Centre for Epidemiologic Studies Depression Scale, Symptom Checklist, Beck Depression Inventory, Self-Rating Anxiety Scale, Self-Rating Depression Scale, Brief Symptom Inventory, Composite International Diagnostic Interview, Memorial Anxiety Scale for Prostate Cancer and the Effects of Prostate Cancer on Lifestyle Questionnaire

Identifying Research Evidence

Data searches were conducted between June 2011 and August 2011. The search protocol was subsequently re-run in June 2013 to ensure no additional data were identified. We searched 6 electronic databases (OVID Medline, EMBASE, AMED, PsycINFO, CINAHL and Web of Science) for articles that met the previously discussed criteria using pre-specified MESH terms as that included Prostate Neoplasm (EXP)” OR “Prostate Cancer” AND “Depression (EXP)” or “Anxiety (EXP)” or “Psychological distress (EXP” or “Stress (EXP)” or “Distress (EXP)”. No restrictions on publication dates were imposed.

To supplement the electronic searches we also conducted searches of the reference lists of previous reviews, key papers and other relevant articles identified by the electronic search. We also conducted systematic searches of the content lists of key journals to identify any additional studies missed by the electronic search.

Study Selection

Titles and abstracts were initially assessed for eligibility. If it was possible to confirm that an article met the inclusion criteria from the abstract alone, the full text article was retrieved. If it was clear from the abstract that an article was not eligible, it was rejected immediately. If it was not possible to determine the eligibility of an article from the abstract, the full text article was retrieved. If any key information was missing, we contacted the authors for the missing data. If this was not possible or ineffective, the study was rejected, (see Figure 1).

Data Extraction

The following specific information relating to data collection and results was extracted individually from each identified article and entered into a pre-designed Excel spread sheet: date and geographical location of data collection; aims and objectives of the investigation; study design; participant inclusion and exclusion criteria; recruitment procedures; sample size; disease stage; socio-demographic status (age, ethnicity and relationship, educational and employment status); time since diagnosis; additional co-morbidity; stage of treatment (pre, on or post-treatment); treatments undertaken (surgery, radiotherapy, hormone therapy, chemotherapy, active-surveillance/watchful waiting); questionnaires utilised; statistical analyses performed; depression prevalence (%) and anxiety prevalence (%).

To test the consistency of data extraction across the studies, three researchers (SW, LL, SE) extracted data from the same 6 randomly selected articles then compared the results of their extraction. A points system was utilised to allow for the objective assessment of consistency. 1 point was allocated for variables with identical data extraction and 0 points for variables with differences. Across all ratings, consistency ranged from 92% to 96% (median: 94%).

Meta-Analysis Procedure

Given the range of estimated proportions expected within the extracted data, the logits of proportions method of conducting the statistical analysis was employed, rather than utilising normal approximations of binomial distributions.

Cochran's Q test was applied to the logits to test the hypothesis of homogeneity of the within study estimates of the proportions, with larger Q values suggesting that the estimates are not homogeneous. Initial analyses highlighted Q values between Q= 15.2 and 215, with some of the larger values suggesting a degree of heterogeneity, the result in some cases of only one or two studies being out of line with the others. For completeness, meta-analysis results have been provided even for those cases where heterogeneity is evident.

Results

Search Results

The electronic database searches initially yielded 1778 journal article references. 1655 of these were subsequently removed due to either duplication or a failure to meet the inclusion criteria. Full text articles were then retrieved and critically appraised for the remaining 123 journal references. Of these 123 articles 97 did not meeting the inclusion criteria. The remaining 26 articles were entered into the meta-analysis.

Hand searches of the key journals identified by the electronic database search revealed no additional journal articles. Searching the reference lists of articles identified through the electronic database search identified 2 journal article references of interest that had otherwise been missed. Full text articles were retrieved for these 2 references, one of which could be included making the total included 27. (Figure 1).

INSERT FIGURE 1

Study Locations

Of the 27 studies entered into the review, 9 were conducted within America (6,8,9,10, 11,12,13,14,15), 4 in both Australia (16,17,18,19) and Holland (20,21,22,23), 3 in the UK (24,25,26), 2 each in Sweden (27,28), Germany (29,30) and Canada (31,32) and 1 in Finland (33). An overview of the key features of each of the included studies can be seen in Table 1.

INSERT TABLE 1

Study Sample Sizes

The samples sizes of the studies entered into the review varied widely from 36 to 861. The total sample size across all 27 studies was 4494 with a mean sample size of 158. The sample sizes of the individual treatment stage groups (pre, on and post-treatment) can be seen in Table 2.

Participant Age

Data on participant age was reported by 24 of the 27 studies and in all 24 cases mean age was reported. The range of mean ages across the 24 studies varied from 57.5 years to 73.2 years. The mean age of all participants across the 24 studies was 66.3 years (3.3). Three

studies failed to report participant age in any format. The mean age of the participants in each of the three treatment groups can be seen in Table 2.

Cancer Staging

Data regarding participant cancer stage was reported by 23 of the 27 studies. There was a general lack of consistency regarding reporting methods. Several studies utilised the clinical T-staging system of T1 (localised) to T4 (metastatic) whilst the majority simply graded PCa as localised, advanced or metastatic. No study reported patient disease stage using the recommended tumour-nodes-metastasis (TNM). The majority of patients had been diagnosed with localised disease (n=3270), followed by advanced (513) and metastatic PCa (87), as shown in Table 2.

INSERT TABLE 2

Cancer Treatments Undertaken

Table 3 provides an overview of the number of participants undergoing each PCa treatment. Unfortunately, it was not possible to stratify the treatments undertaken as a function of either disease stage (localised, advanced or metastatic) or treatment stage (on-treatment or post-treatment). This was because in many instances patients with different disease staging or who were at different treatment stages were recruited into the same cohort. Consequently, whilst the number of patients completing each type of treatment was clearly highlighted, it was not possible to determine whether the patients with localized, advanced or metastatic disease, nor those who were either on or post-treatment, had completed them. Thus the data in Table 3 provides a collective overview of the treatments undertaken by all of the patients, irrespective of disease or treatment stage. Additionally, several of the pre-treatment studies recruited participants who had yet to decide upon treatment. Such patients are listed in Table 3 as 'newly diagnosed'.

INSERT TABLE 3

2.6. Questionnaires Analysis

Of the 12 questionnaires meeting the questionnaire inclusion criteria as listed in the method section, only 7 were utilised by the 27 studies entered into this meta-analysis. Table 4 lists the 7 questionnaires, the frequency with which they were used and the clinical cut-off scores utilized to determine caseness.

INSERT TABLE 4

Meta-Analysis of Depression and Anxiety Prevalence

Number of studies reporting depression

26 of the 27 studies entered into the review reported data on depression prevalence. Of these 26, 13 reported depression in pre-treatment patients, 9 in on-treatment patients, and 13 in post-treatment patients. The number of total studies from the 3 groups exceeded 27 as several longitudinal studies reported depression in multiple treatment groups (i.e. in both pre-treatment and on-treatment groups).

Number of studies reporting anxiety

20 of the 26 studies entered into the review reported data on anxiety prevalence. Of these 20, 9 reported anxiety in pre-treatment patients, 4 in on-treatment patients and 11 in post-treatment patients.

Number of Patients Measured for Depression

Collectively, measures of depression were recorded from 5139 participants across the 26 studies. In terms of the individual treatment groups, 1259 participants provided measures of depression in the pre-treatment group, 723 in the on-treatment group and 3157 in the post treatment group.

Number of Patients Measured for Anxiety

Collectively, measures of anxiety were recorded from 4635 participants across the 20 studies. In terms of the individual treatment groups, 1057 participants provided measures of

anxiety in the pre-treatment group, 501 in the on-treatment group and 3077 in the post treatment group.

Pre-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of depression was 17.27% (CI: 15.06%-19.72%).

Anxiety: Within the 9 studies that provided measures of anxiety in PCa patients prior to undergoing treatment (see Figure 1), the prevalence of anxiety was 27.04% (CI: 24.26%-30.01%).

INSERT FIGURE 2

On-Treatment Depression and Anxiety Prevalence

Depression: Within the 9 studies that provided measures of depression in PCa patients currently undergoing treatment (see Figure 2), the prevalence of depression was 14.70% (CI: 11.92%-17.99%).

Anxiety: Within the 4 studies that provided measures of anxiety in PCa patients currently undergoing treatment (see Figure 2), the prevalence of anxiety was 15.09% (CI: 12.15%-18.60%).

INSERT FIGURE 3

Post-Treatment Depression and Anxiety Prevalence

Depression: Within the 13 studies that provided measures of depression in PCa patients who had completed treatment (see Figure 3), the prevalence of depression was 18.44% (CI: 15.18%-22.22%).

Anxiety: Within the 11 studies that provided measures of anxiety in PCa patients who had completed treatment (see Figure 3), the prevalence of anxiety was 18.49% (CI: 13.81%-24.31%).

INSERT FIGURE 4

Depression and Anxiety Prevalence Across and Within Treatment Groups

Figure 4 provides a pictorial representation of the prevalence of depression and anxiety both within and across each of the three treatment groups.

INSERT FIGURE 5

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Discussion

There is a real need within clinical oncology, particularly as the burden of disease is escalating with improved diagnosis and treatment, for an increased awareness about the issue of psychological distress among men diagnosed with, being treated for and surviving through/living with a PCa diagnosis. The results of the current meta-analysis go some way in addressing this issue by providing those working within the field of PCa with a rigorous overview of the likely prevalence of depression and anxiety in the patients they treat.

Our findings suggest that over the trajectory of the PCa journey, depression and anxiety prevalence are highest in patients who have yet to undergo treatment (17.27% and 27.4% respectively), lowest in patients who are currently undertaking treatment (14.70% and 15.90% respectively) before rising again in patients who have completed treatment (18.44% and 18.49% respectively). The relatively small variation observed within these prevalence rates across the different treatment stages, along with the large collective sample size of the meta-analysis (4494) suggests these conclusions are valid, powerful and robust summaries

of the data available. The prevalence of clinical depression and anxiety in British men aged over 65 years is estimated to be less than 9% and 6%, respectively (34). Such data are in stark contrast to the prevalence reported in PCa patients of the same age in this study.

The current meta-analysis is the first of its kind to specifically assess the prevalence of clinical depression and anxiety in prostate cancer (PCa) patients over their treatment spectrum, from pre-treatment, through treatment to post-treatment follow up. To date, the lack of synthesis of the available data relating to depression and anxiety in PCa has meant that clinical decisions have been based on isolated research trials that lack sufficient power and depth in terms of sample sizes, treatment protocols and treatment stages. Consequently the true prevalence of psychological morbidity experienced by PCa patients across the treatment spectrum is poorly understood and described and this may result in patients being left untreated.

We hope that with additional epidemiological investigation we will be able to offer a more risk adapted approach with more intensive screening and support being offered to individuals who are most at risk of psychological morbidity which may in part be related to their current stage of treatment. This is important as research suggests that cancer patients who are suffering from clinical depression and anxiety are less likely to adhere to their treatment plan and are more likely to experience adverse reactions to their treatment (4,5). Indeed, recently published research has specifically highlighted the negative impacts of PCa specific anxiety on post-treatment survivorship in the form of poorer sexual function and increased depressive symptomology, further supporting the need for effective and timely intervention (35).

Consequently, the identification, treatment and management of concurrent psychological distress should be a key clinical objective as a means of enhancing both clinical outcomes and patient quality of life. Identifying which stage of treatment PCa patients are most likely to experience such conditions is an important first step to achieving this.

There are several limitations to the results generated by this review that need to be noted when interpreting the findings. There is a noticeable dearth of research into the prevalence of depression and anxiety in PCa patients with metastatic disease; we identified only 87 patients with metastatic PCa, out of the pooled sample size of 4494. Given the increased physical symptomology, and significantly lowered life expectancy, associated with metastatic PCa, it is possible that the prevalence of psychological morbidity within this patient cohort will probably be substantially higher. Unfortunately it was not possible to generate depression and anxiety prevalence data specifically for men with metastatic disease as the studies that recruited PCa patients with metastatic disease did so as part of larger collective

samples of patients that included those with localized and/or advanced PCa. In the majority of cases, no individual depression and anxiety data were provided specifically for those with metastatic disease. Consequently it was not possible to describe these patients separately.

We do not know the overall proportion of men who suffer from some psychological distress during their PCa cancer journey from these largely cross-sectional studies. We suspect that a number of individuals become depressed and anxious at various stages of their cancer journey and then may improve so overall the numbers of people affected at some stage may be higher than we are able to identify from this analysis. We would need to conduct a sustained longitudinal cohort study to resolve this question. Likewise, none of the included studies provided any form of data relating to the patients past history of depression and anxiety. Consequently it was not possible to determine whether a past history of depression and anxiety acted as a significant predictor of current depression and anxiety.

Furthermore this study did not compare the depression and anxiety prevalence rates generated directly to that observed in a cohort to healthy men or men with other cancers. As a consequence we were unable to specifically determine how PCa and its treatment impacted upon the prevalence of psychological distress observed. The essentially descriptive nature of this study therefore needs to be noted.

It is also important to note the wide variability in both the point prevalence estimates of anxiety and depression and the 95% confidence intervals associated with them. There are likely to be many reasons for this variability which include sample size, the differing instruments that have been used to measure depression and anxiety, selective populations and post-treatment outcomes. For example, it is possible that depression and anxiety prevalence in post-prostatectomy patients would vary substantially depending upon factors such as positive or negative margin status. Unfortunately it was not possible to formally investigate the properties of the populations to determine whether there were any such differences that would explain this variability. This represents an important limitation to the findings of this study. It is important that future studies into the assessment of depression and anxiety in this patient group carefully identify the characteristics of their populations to address this issue.

We were also not able to determine whether the prevalence of depression and anxiety was a factor influencing the type of PCa treatments provided to individuals. The associated side effects of PCa treatment include debilitating urinary, sexual and bowel dysfunction as well as the potentially negative psychological side effects of passive treatment options such as active surveillance (AS) and watchful waiting (WW), in which the patient faces living with a diagnosed but untreated cancer. This is an important clinical issue as it may provide a novel

avenue in which to streamline the screening of depression and anxiety by offering patients undertaking treatments that have been shown to induce higher rates of distress with early, preventive support during their cancer journey.

Burnett et al (2007) reports that the prevalence of depression among AS/WW patients is just 4% (in a sample of 100 patients recruited from a single cancer centre of international excellence), leading the authors to conclude that AS does not predispose patients to higher levels of distress in comparison to those undergoing radical treatment. However our data identified that the prevalence of depression is almost three times higher than that reported by Burnett et al (2007) at 11% (within this specific population, suggesting that psychological distress may indeed be a substantial risk associated with AS/WW.

The utilisation and uptake of AS/WW within the UK is increasing (36), yet our results clearly highlight that the issue of psychological morbidity among these PCa patients is poorly described and defined, with only 4 of the 27 studies entered into this review obtaining measures of depression and anxiety from this patient population (21,22,26,33). Consequently we suggest that patients being treated with AS/WW should be investigated in more detail to better understand the psychological ramifications of this form of management. Such research should ideally involve the recruitment of larger sample sizes (>200) from multiple sites to provide a more generalisable estimate of psychological distress from this patient cohort.

In conclusion, across the treatment spectrum, PCa patients appear to experience a moderate to high degree of psychological morbidity ranging from 15% to 27%. Most acute prevalences of depression and anxiety occur prior to and after the completion of treatment, the consequences of which may go on to negatively impact upon treatment compliance (6), increased periods of hospitalisation (5) and overall functional quality of life (37). Based on our findings we conclude that the assessment, diagnosis and treatment of depression and anxiety should be a key priority for any clinical oncology team working with PCa to enable them to optimise their patients' quality of life and clinical treatment outcomes.

Authors Contribution

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Tables

Table 1: Key features of the included studies

Author	Year	Location	Sample size	Participant Age	Cancer stage	Treatment stage
Ene	2006	Sweden.	123	63.1	No data provided	Pre to Post-treatment
Pirl	2008	USA.	50	62	Advanced	Pre and On-treatment
Sharpley	2007	Australia.	195	69.2	Localised	Post-treatment
Bisson	2002	Wales	83	64.5	Mixed	Pre-treatment
Dirkson	2009	USA	51	73.4	Mixed	On-treatment
Dale	2009	USA	67	67.9	No data provided	Pre-treatment (but all participants had received prior primary therapy)
Gabershagen	2007	Germany	115	64.1	Localised	Pre-treatment
Gabershagen	2009	Germany	84	62.8	Mixed	Pre-treatment to post-treatment
Hervouet	2005	Canada	861	67.9	Mixed	Post-treatment
Monga	1999	USA	36	66	Localised	Pre-treatment to On-treatment to Post treatment
Monga	2005	USA	40	67.8	Localised	Pre-treatment to On-treatment to Post-treatment
Pirl	2002	USA	45	69.4	Localised and Metastatic	On-treatment
Savard	2005	Canada	327	66	localised	Post-treatment
Stone	2000	England.	62	69	Mixed	On-treatment
Soloway	2004	USA	103	62	No data provided	Pre-treatment
Steineck	2002	Finland	326	64.5	Localised	Post-treatment
Symon	2006	USA	50	59.9	Localised	Pre-treatment to Post-treatment
Sharpley	2007	Australia.	183	69.2	Localised	Post-treatment
Sharpley	2009	Australia.	150	69.8	Localised	Post-treatment
van Tol-Geerdink	2006	Holland	118	70	Localised	Pre-treatment
Van den Berg	2009	Holland	129	64.9	Localised	On-treatment (active surveillance)
Van den Berg	2010	Holland	129	64.6	Localised	On-treatment (active surveillance)
Monga	2001	USA	40	67.6	Localised	Pre-treatment to Post-treatment
Korfage	2006	Holland	299	65.4	Mixed	Pre-Post treatment
Bitsika	2009	Australia	381	No data	Localised	Post-treatment
Nordin	2001	Sweden	118	No data	Localised & Advanced	Pre-treatment
Burnet	2007	England	329	68.8	Localised	On-treatment and post-treatment

Table 2: Overview of Study Characteristics

	All studies	Pre-Treatment Studies	On-Treatment Studies	Post-Treatment Studies
Study Samples (patient numbers)	4494	1707	723	3087
Participant Ages	66.3 (3.3)	64.8 (2.9)	67.6 (3.3)	66.9 (2.4)
Number of patients with localised PCa	3270	1299	563	2236
Number of patients with advanced PCa	513	162	72	441
Number of patients with metastatic PCa	87	58	40	7

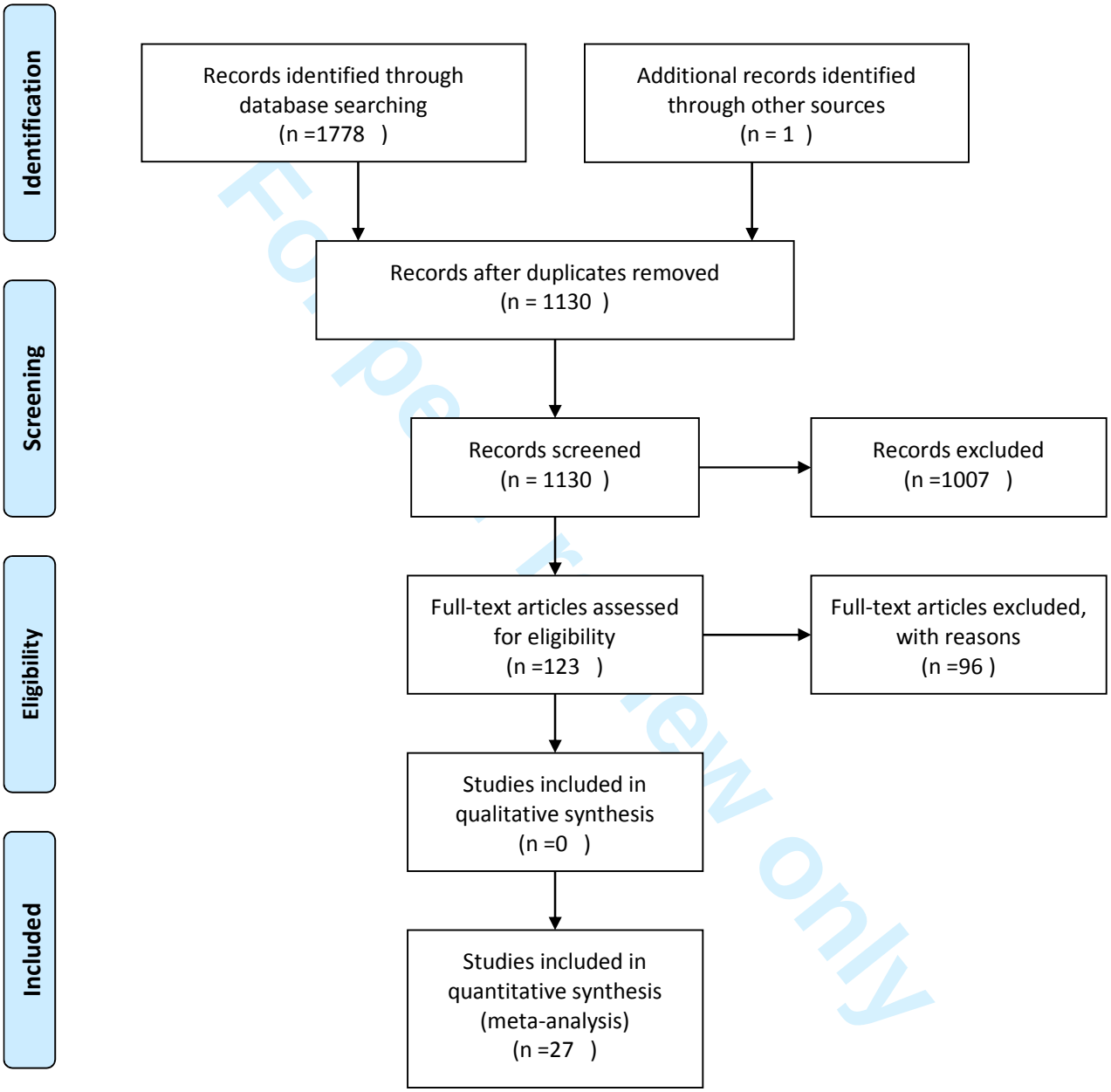
Table 3. The number of PCa patients being treated and undertaking each treatment modality

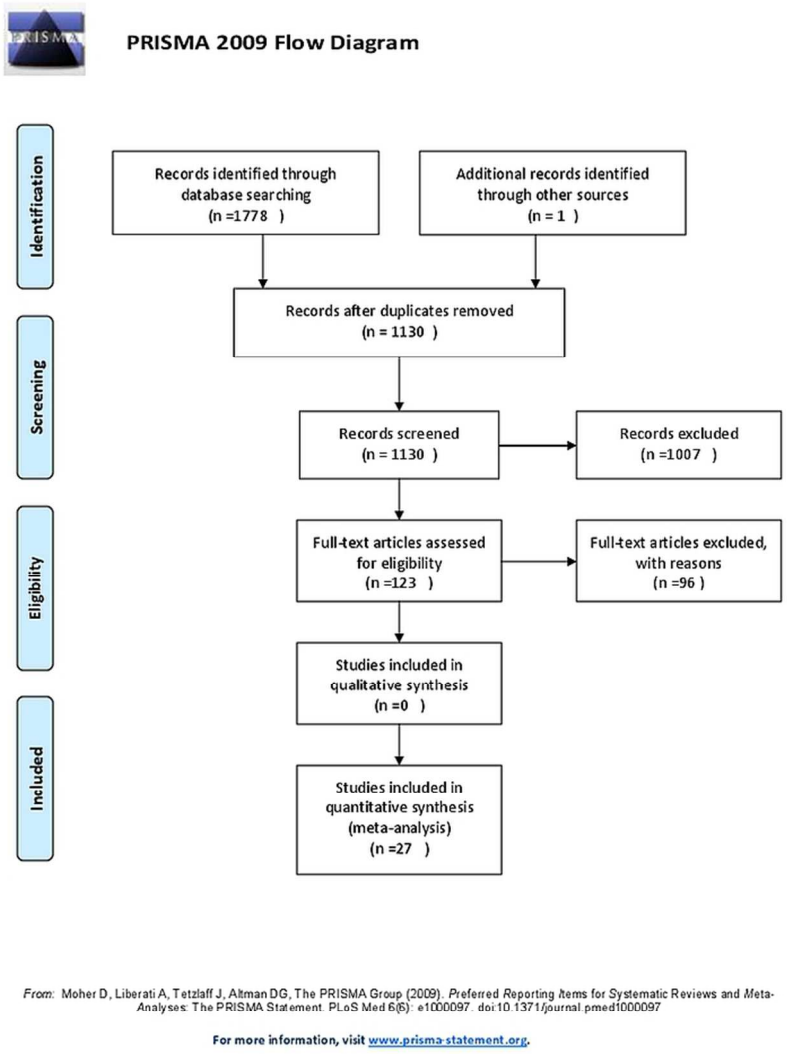
Radical Prostatectomy	Radiotherapy (EBRT & Brachytherapy)	Hormone Therapy (orchiectomy and ADT)	Chemotherapy	Active Surveillance or Watchful Waiting	Newly diagnosed (no treatment yet selected)
924	1578	264	24	418	304

Table 4. Questionnaires utilised , frequency of use and cut-off scores utilized

Questionnaire Name	Frequency of Use	Clinical Cut-Off Scores Utilised
Hospital Anxiety and Depression Scale (HADS)	13	HADS-A: ≥8 HADS-D: ≥8
Beck Depression Inventory (BDI)	6	≥10
Self Rating Anxiety Scale (SAS)	4	≥36
Self Rating Depression Scale (SDS)	4	≥40
Centre for Epidemiologic Studies Depression Scale (CES-D)	4	≥15
Stait-Trait Anxiety Scale (STAI)	4	≥44
Memorial Anxiety Scale for Prostate Cancer (MAX-PC)	3	≥27

Figure 1: PRISMA 2009 Flow Diagram





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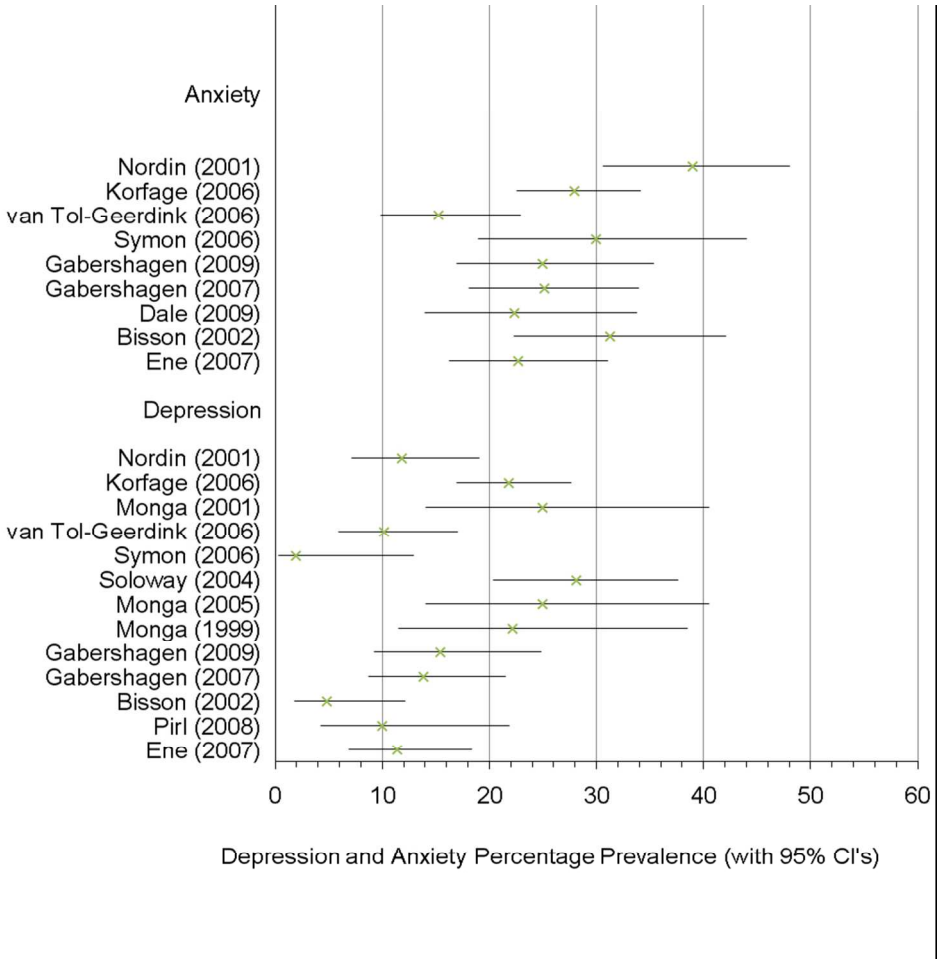

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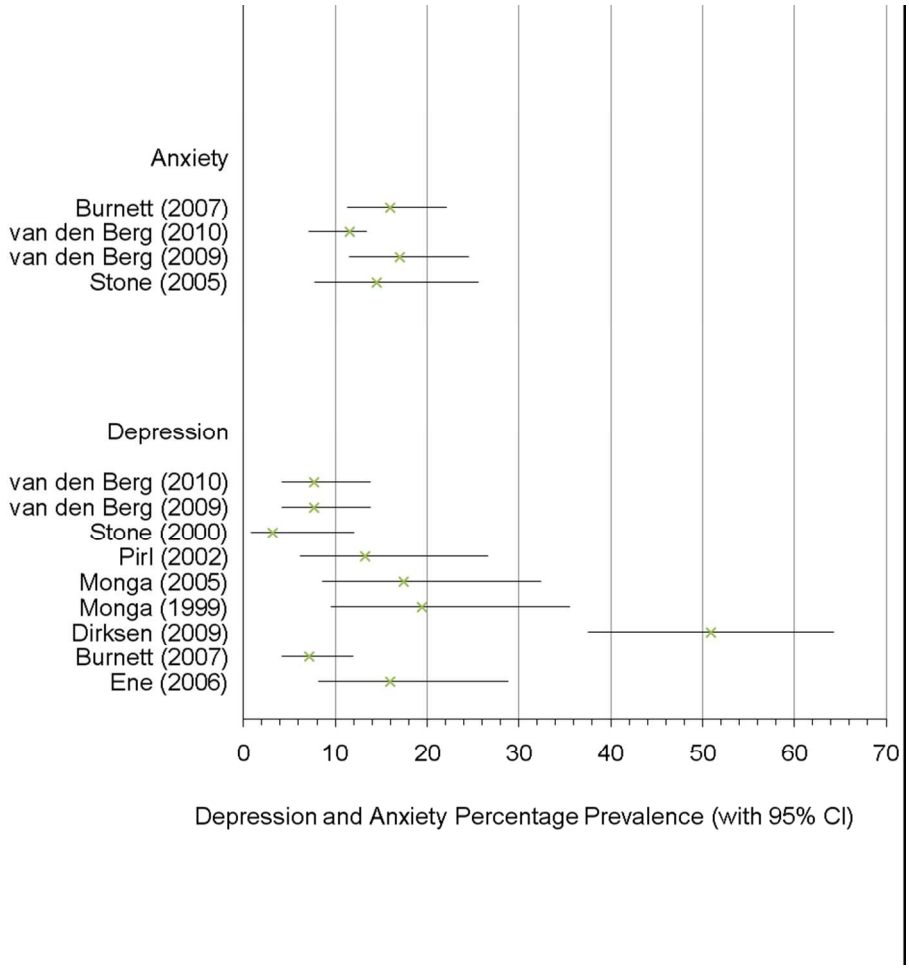

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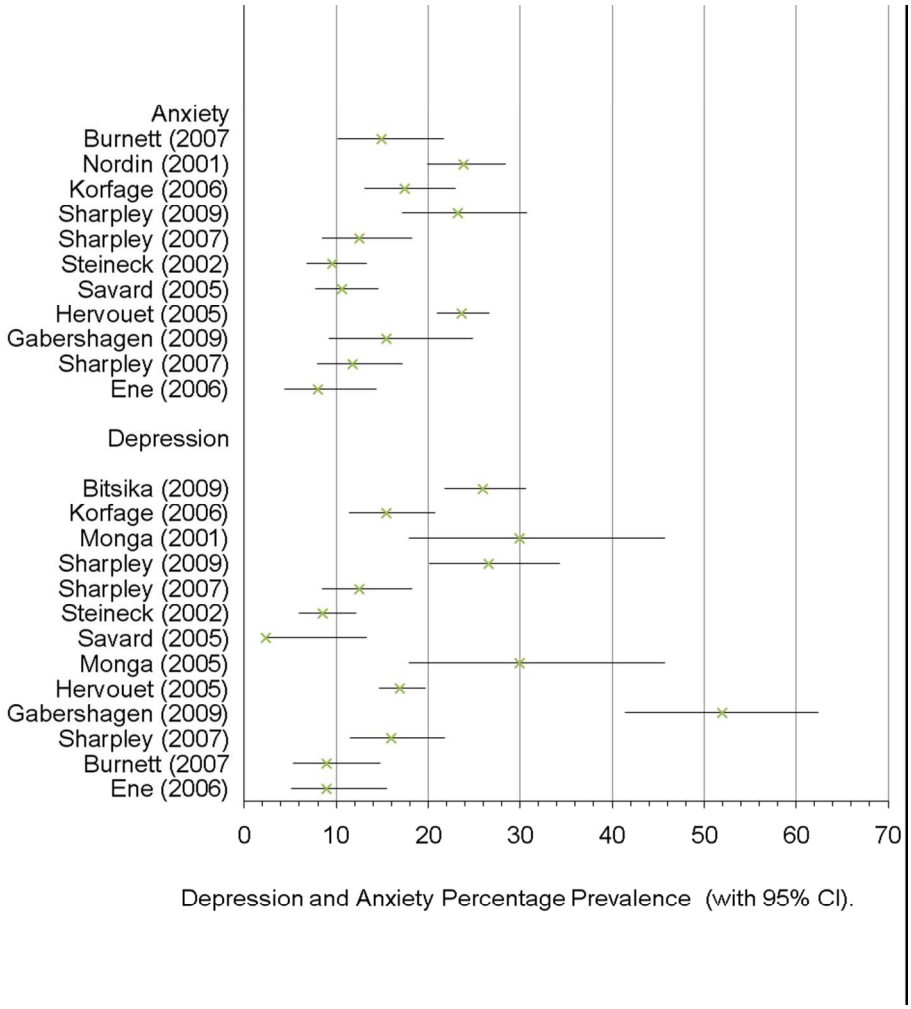

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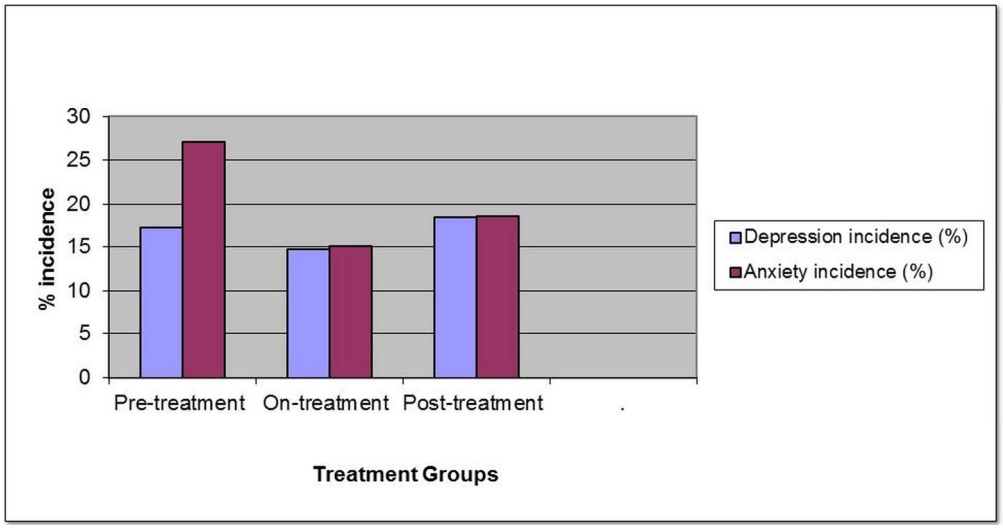

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PRISMA 2009 Checklist

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
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	NA
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
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.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
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).	6
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.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
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.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
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.	7

PRISMA 2009 Checklist

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).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
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.	7
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.	8-9
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).	NA
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.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
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).	12
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).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
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.	3

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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