Sustained benefit of cognitive behaviour therapy for health anxiety in medical patients (CHAMP) over eight years: randomised controlled trial

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Abstract

 Background: Health anxiety is an under-recognised but frequent cause of distress that is treatable. It is particularly common in general hospitals.

Methods: We carried out an eight year follow-up of medical out-patients with health anxiety (hypochondriaisis) enrolled in a randomised controlled trial in five general hospitals in London, Middlesex and Nottinghamshire. Randomisation was to a mean of 6 sessions of cognitive behaviour therapy adapted for health anxiety (CBT-HA) or to standard care in the clinics. The primary outcome was change in score on the Short Health Anxiety Inventory, with generalised anxiety and depression as secondary outcomes. Of 444 patients aged 16-75 seen in cardiology, endocrinology, gastroenterology, neurology and respiratory medicine clinics 306 (68.9%) were followed up 8 years after randomisation, including 36 who had died.  The study is registered with [controlled-trials.com](http://controlled-trials.com/), ISRCTN14565822.

Findings: There was a significant difference in HAI score in favour of CBT-HA over standard care after eight years (1.83, 95%CI=(0.25,3.40), P=0.023) and although between group differences in generalised anxiety were less (0.54, 95%CI= (-0.29,1.36)), P=0.20), those for depression were greater at 8 years (1.22, 95%CI= 0.42, 2.01, P<0.003,) in CBT-HA than in standard care, with most of those allocated to standard care satisfying the criteria for clinical depression. Patients seen by nurse therapists and those in cardiology clinics achieved the greatest gains with CBT-HA.

Interpretation:  CBT HA is a highly effective treatment for pathological health anxiety with long-term benefits.  Standard care for health anxiety in medical clinics is not beneficial.

***Introduction***

Pathological health anxiety is a growing problem in all medical settings, and is likely to increase in prevalence as people are encouraged to take more responsibility for their heath. It has suffered through being regarded for many years as identical to hypochondriasis and disorders of somatic symptomatology 1-2.  People with abnormal health anxiety fear undetected medical illness, leading to frequent medical consultations, requests for tests, reassurance from other health professionals and even relatives, to exclude the feared disease.  Previous trials have demonstrated the benefits of cognitive behaviour therapy in patients in primary care, both in direct face to face or group treatment3-5 and by internet-directed or web-based treatment6-9. Almost all of these studies have been with patients who are already aware that they have health anxiety. This is very different from the circumstances in secondary medical care where so many of these patients have had medical illnesses and present without realising their fears are pathological.

In the CHAMP trial these latter patients were recruited to a randomised trial of cognitive behaviour therapy adapted for health anxiety or standard care in the clinics. After two years greater clinical benefit for anxiety symptoms was found in the CBT-HA group with partial cost offset for the treatment given10. Because benefits were sustained the study was extended up to 8 years of follow-up after randomisation.

***Method***

The CHAMP study (Cognitive behaviour therapy for Health Anxiety in Medical Patients) was a pragmatic randomized controlled trial. It had two parallel arms with equal randomization of eligible patients to (i) 5-10 sessions of cognitive behaviour therapy adapted for health anxiety (CBT-HA) or (ii) standard care as usual in the clinics. The primary outcome was set as reduction of symptoms of health anxiety, measured by the Short Health Anxiety Inventory (SHAI), after one year10, but the intention at the outset was to carry out long term follow up as there was uncertainty about the stability of health anxiety over time.

As this was a pragmatic trial those allocated to CBT-HA were treated by professionals who might readily be available in hospital settings, including graduate research workers, nurses or related health professionals. Those interested were trained for this intervention in advance by attendance at two workshops, and during treatment were supervised by experienced staff. Therapists were not randomised and each patient allocated to CBT-HA was seen by the next available therapist.

The two main initial hypotheses, based upon the results of a pilot study,11 were that patients in the CBT-HA group would have lower levels of health anxiety (SHAI scores) one year after randomisation to the trial than those treated in standard care and that, from a health and social care perspective, the costs of the CBT-HA and standard groups would be equivalent at 2 years (i.e. costs of CBT-HA would be offset by savings in other areas).

Assessments of health anxiety, generalised anxiety, depression, social function, quality of life and costs were made over a two year period after randomization.

Several secondary hypotheses were also tested, including that health anxiety at other time points, generalised anxiety and depression, and social functioning would also differ between CBT-HA and standard care.

***Randomisation and masking***

Eligible patients who gave consent to be randomised were allocated in a 1:1 ratio to the two arms of the study according to a computer-generated random sequence using block randomisation with varying block-size of four and six. This was carried out independently with the allocation sequence not available to any member of the research team until final analysis. Research assistants who collected data had no knowledge of allocation at any time.

***Settings and procedure***

Patients attending cardiology, endocrine, gastroenterology, neurology and respiratory medicine clinics, in six general hospitals in the UK covering urban, suburban and rural areas, were considered for the study. All patients attending clinics of the collaborating consultants, apart from the specific exclusions below, were approached while waiting for their out-patient appointments and, after consent, given the SHAI,12 a self-rating scale of 14 questions that takes 5-10 minutes to complete. Those that scored 20 or more on the scale, a point that has been shown to discriminate between persistent worry over health and normal variation12-13 were given a brief summary of the trial and offered the opportunity of further assessment, and, if they were interested, were then given an information sheet about the study. Those that agreed in principle to take part were then asked the questions in the Structured Clinical Interview for DSM-IV14 covering the diagnosis of hypochondriasis. Those that satisfied the diagnosis of hypochondriasis were asked for written consent to take part and baseline assessments completed. This, through necessity, involved a standard explanation of the nature and significance of health anxiety and so constituted a small intervention in all patients who entered the trial. After baseline assessment, randomization was carried out by an independently operated computerised system.

***Interventions***

Each patient in the CBT-HA arm of the trial was offered between 5 and 10 sessions of treatment initially but booster sessions were also allowed, though few were taken up. Each therapist was supervised at least at 2-4 week intervals during treatment to ensure consistency in treatment. Possible bias in follow-up assessments was reduced by replacing the research assessor with another research assistant if at any time they were unwittingly informed about the patient’s allocation status.

**Training and Fidelity of Intervention**

Four senior members of the CHAMP team trained the therapists at two workshops and also assessed treatment fidelity. 50% of all treatment sessions were audio recorded. Fidelity was tested using the health anxiety modification of the Cognitive Therapy Rating Scale (CTRS-HAV). 17 Recordings were assessed by the local supervisor and a random sample sent to a supervisor at a different site to assess the level of agreement, with further training ending only when an agreement level of 0.80 kappa was reached. An independent assessor involved in the development of the treatment (Hilary Warwick) assessed any discordant ratings. Only one of the 17 therapists failed to reach the level of competence; this person saw only five patients10.

The study was approved by the North Nottingham Ethics Committee (08/H0403/56) before data collection started.

***Inclusion and exclusion criteria***

Those who satisfied the criteria for excessive health anxiety above were included if they were (i) aged between 16 and 75, (ii) permanently resident in the area, (iii) had sufficient understanding of English to read and complete study questionnaires, and (iv) gave written consent for the interviews, audio-taping of 50% of treatment sessions, and for access to their medical records. The presence of existing medical pathology, provided it was not a new diagnosis requiring further investigation, was not an exclusion criterion. Those with continuing major pathology that was considered too severe for them to take part in the study, including progressive cognitive impairment, terminal disorders, and any major comorbid pathology that would interfere with psychological treatment, and those currently under psychiatric care were also excluded.

***Assessments at baseline and at intervals to eight years***

Over the course of the eight year follow up a standard set of assessments was carried out by research assistants unaware of treatment allocation. This was administered at baseline, 6m, 12m, 24m, 5 years and 8 years. Some others, particularly linked to cost-effectiveness, could not be included at all time points. Health anxiety (SHAI),12 anxiety and depression (HADS),15 and social function (SFQ)16 were selected as the standard assessment set; all of these were self-ratings.

The component of the study reported here was an eight-year follow-up, and was given extra weight by the fact that CBT-HA was not generally available in the NHS so that none of the patients in standard care received this particular treatment over the eight-year period.

The trial recruited 444 patients (219 to CBT-HA, 225 to standard care) between October 2008 and July 2010 from cardiology, endocrinology, gastroenterology, neurology and respiratory medicine clinics in five general hospitals in England.

 The difference between the mean score on the short form of the Health Anxiety Inventory (SHAI) between baseline and eight years was the primary outcome in this follow-up study, as indeed it was at all previous times of assessment. Secondary outcomes included changes between scores in the two groups at 8 years for (i) changes in the HAI, HADS, and SFQ scores at 8 years and overall.

*Statistical measures and outcomes*

The primary endpoint was analysed using a mixed model with time, treatment, and time x treatment interaction as fixed effects, baseline measurement as covariate, and patient as random effect. Missing data were treated as missing at random in the mixed model analysis. To assess the sensitivity of the result to missing values, the last observation carried forward (LOCF) strategy was used to compute the missing HAI at the follow up visits. Other assessments were analysed in a similar way. In addition, covariate-adjusted analysis was performed on the primary outcome analysis by a mixed model controlling for 3 pre-specified potential predictors for primary endpoint (clinic type, site and age).

All statistical analyses were based on  he intention-to-treat principle using the statistical package SAS 9.3. Deaths were reported separately for each group.  The CONSORT procedure was used for reporting patient flow through the trial and has been published previously17.

***Results***

[Figures 1 & 2 and Tables 1-3 near here]

217 patients were randomized to CBT-HA and 225 to standard care. 74% had an established physical diagnosis at baseline. Patients were not randomised to therapists and were allocated on the basis of availability. Attrition rates and follow-up using the CONSORT procedure at 5 years have been reported earlier17 when 308 patients provided data. At 12 years there were 36 deaths, 20 in the CBT-HA group (mean age at death 61.1y) and 16 in the standard care one (mean age at death 60.1y). The number of treatment sessions with CBT-HA was set originally at 6 but extra sessions were given if agreed by therapist and supervisor, and overall a mean of 6.0 sessions (range 0-22) was given. The full results at two years have been reported previously10; for the primary outcome (HAI score difference between groups at 1 year) the reduction in health anxiety was 2.97 points more in the CBT-HA group than in standard care (P<0.0001). These differences were maintained throughout follow-up. After eight years there was still a clear significant difference in adjusted HAI score in favour of CBT-HA over standard care (1.83, 95%CI=(0.25,3.40), P=0.023)(Table 1), with no loss of efficacy between 2 and 8 years (Figure 1).

The findings between groups for generalised anxiety using the HADS anxiety scale were not significant after eight years (0.54, 95%CI= (-0.29,1.36)), P=0.20, ns)(except in endocrinology patients) but HADS depression scores showed a mean gain of 1.22 points in those treated with CBT-HA compared with standard care (1.22, 95%CI= 0.42, 2.01, P<0.003); this related to an increase in depression in those in standard care (Table 1). The mean score for HADS depression at 8 years in those allocated to standard care was 9.6, well within the category of clinical depressionref Social functioning also showed some evidence of benefit in those allocated to CBT-HA at 8 years (mean difference 0.53, 95%CI= (-0.04, 1,.11) (P<0.07)(Table 1).

Table 2 displays the results from mixed model analysis of clinical outcomes at 5 and 8 years after imputation of missing outcomes using last observation forward strategy. The results remain similar to those from crude and adjusted analysis in Table 1. The findings remained similar after using multiple imputation by means of PROC MI in the SAS package.

*Therapist differences*

17 therapists were involved in treatment; of the 219 patients allocated to CBT-HA, 87 were seen by assistant psychologists, 66 to other health professional graduates, and 66 to general nurses who had received no previous training in cognitive behaviour therapy.

After 8 years 128 patients in the CBT-HA group were assessed, but 20 had died, all from natural causes. 60 (69%)(excluding 10 deaths) of those treated by assistant psychologists, 35 (53%)(excluding 3 deaths) by graduate therapists, and 33 (50%)(excluding 7 deaths) by nurses. The outcome by therapist type is shown in Table 3. Reduction in health anxiety scores (mean improvement 6.26, 95%CI=(3.70, 8.81), P<.0001), generalised anxiety (mean improvement 2.67, 95%CI=(1.07,4.28), P=0.0011), depression (mean 1.75 improvement, 95%CI=( (0.10,3.40), P=0.0378), and social functioning scores (mean improvement 1.22, 95%CI=( (0.04,2.41), P=0.0425), were all significantly greater in the nurse-treated patients than in other therapy groups (graduates and assistant psychologists).

*Adverse events*

All the 36 deaths occurring during the trial were from natural causes; one patient in standard care made a serious suicide attempt 6 months after randomisation.

***Discussion***

The results of this trial demonstrate a sustained benefit for a brief psychological treatment given for a mean of only 6 sessions. This finding is robust and does not allow for any other explanation apart from continued efficacy, and is confirmed by appropriate statistical adjustment.  Although the reasons for the maintenance of significant differences between CBT-HA and standard care cannot be determined formally it is possible, and may be likely, that standard care has a negative influence on health anxiety, as the normal resolution of untreated anxiety in long-term trials was not shown.  In ordinary practice health anxiety is likely to be continually reinforced by a combination of reassurance and continued tests, which are mainly unnecessary but still promote the belief that the hospital staff must think there is an underlying disease. As a score on the SHAI of 10 can be regarded as normal (as it is wise to have some concern for your health), and one of 20 is pathological, the 2 point difference between scores at 8 years is likely to be clinically as well as statistically meaningful.

 The increase in depressive symptoms in the standard care group over the long follow up also suggests that untreated health anxiety is a disabling disorder. The findings here were not predicted in our original hypotheses, as we predicted that, as depression is often found with hypochondriasis, there might be some initial improvement in these symptoms. What was surprising was the steady increase in depressive symptoms from year 2 of follow-up onwards in the standard care group (Figure 2), suggesting that the repeated strain of taking responsibility for your health takes its toll in the longer term.

The finding that most of the patients in the standard care group were within a band consistent with clinical depression18 suggests that untreated health anxiety carries more risks than mere persistence of the anxiety and should be treated actively. Anxiety disorders are also associated with a three-fold increase in suicidal behaviour19 and the persistence of symptoms makes such behaviour more likely. There may also be other medical consequences of persistent health anxiety.  Anxiety disorders in general lead to premature mortality, and this includes those who have excessive health anxiety after cardiac events20.

The reason for the better outcomes in patients attending cardiovascular clinics may be related to advice given to those with cardiac symptoms, especially chest pain, to consult as soon as possible, and for A&E clinics to give such patients preference when they arrive. This advice is likely to promote health anxiety in susceptible patients and further reinforce symptoms. In the case of gastroenterology there is considerable concern about the high level of health anxiety associated with conditions such as the irritable bowel syndrome and the negative value of reassurance was been noted21. There is also evidence that rates of health anxiety in gastroenterology clinics are increasing22, possibly provoked by Internet browsing for health worries (cyberchondria)23-24 are also likely to be a factor in preventing improvement.

The better outcome in patients allocated to nurse therapists was not expected at the outset and is difficult to explain. Nurses may have been seen as more appropriate therapists than others because of their training and perceived greater knowledge of medicine. If this was true patients would have greater confidence in their judgment when interpreting symptoms. More treatment sessions were given by the nurses than by other groups (a mean of 2.5 more25) and this was associated by fewer drop-outs in this group.

The main limitation of the findings is the selected nature of the participants in the trial.  Only 444 were recruited out of 5224 screened, and most of the remaining 4780 were likely to have been eligible after excluding those who did not satisfy the trial criteria. This suggests that a large proportion of people who might be helped by this treatment are reluctant to try it.  We can only guess what proportion of these reluctant patients might be helped by the treatment, but the excellent response of those who did take part suggests that if there was better awareness of the value of this intervention, it would represent an important opportunity to expand a successful treatment. A similar study in general practice and hospital settings of repeat users of unscheduled care, using very similar methodology to CHAMP, recruited 33% of eligible patients and demonstrated very similar results at both 6 months and one year9. This suggests that our results are reasonably representative of the population at risk.

There is a need for better awareness of this disorder and its associated symptoms. This is not difficult to achieve, especially as our evidence suggests that the necessary expertise can be taught in general hospitals, not only to nurses but all relevant staff. Because so many of the people who attend with these problems want answers from their physicians and nursing colleagues, these staff are best placed to both identify the problem and offer solutions, with mental health providers helping as secondary agencies.

 \* Since the publication of this paper a set of pilot sites has been set up by NHS England to investigate the value of training nurses in CBT-HA in general hospitals.

*Authors' contributions:*

The follow-up study was initiated by PT and HT, who, with MC, BB, SD, and DW designed the structure and the analysis plan. SC was the trial coordinator and organiser of the recruitment strategy. SN and VL carried out the eight year assessments, and BB carried out the economic analysis. Aaron Beck, MD, (the inventor of CBT) acted as trial adviser.  All authors read and approved the final manuscript.

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The full data from this study are available by contacting Peter Tyrer, Michael Crawford (m.crawford@imperial.ac.uk), and Duolao Wang (Duolao.Wang@lstmed.ac.uk), .

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**Figure 1: Mean changes in Short Health Anxiety Inventory (SHAI) scores in 270 patients allocated to CBT-HA (n=128) or Standard care (n=142) over 8 years**



Threshold score for possible clinical depression

**Figure 2: Mean changes in the Depression Scale of the Hospital Anxiety and Depression Scale (HADS-D) in 270 patients allocated to CBT-HA (n=128) or Standard care (n=142) over 8 years.** *A score of 9 is an accepted threshold for the presence of clinical depression18*

**Table 1. Mean changes in summary statistics and results from mixed model analysis of clinical outcomes at 5 and 8 years**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  | Results from mixed model analysis |
|  |  | Summary statistics N, mean improvement from baseline (SD) | Unadjusted analysis \* | Adjusted analysis \*\* |
| Outcomes | Time \*\*\* | CBT-HA  | Standard Care  | Difference (95%CI) | P value | Difference (95%CI) | P value |
|  |  |  |  |  |  |  |  |
| Health anxiety | 5 years | 149, 6.45(8.57) | 158,4.34(7.75) | 2.20(0.68,3.72) | 0.0045 | 2.35(0.84,3.86) | 0.0023 |
| (SHAI) | 8 years | 128, 7.14(7.73) | 142,5.68(7.56) | 1.69(0.10,3.27) | 0.0368 | 1.83(0.25,3.40) | 0.0228 |
|  | Over 8 years |  |  | 2.58(1.49,3.66) | <.0001 | 2.72(1.65,3.79) | <.0001 |
|  |  |  |  |   |  |  |  |
| Generalized anxiety | 5 years | 150, 5.56(5.72) | 158,4.54(5.48) | 0.67(-0.26,1.60) | 0.1596 | 0.70(-0.12,1.52) | 0.0939 |
| (HADS-A) | 8 years | 128, 5.59(5.58) | 142,5.06(5.30) | 0.42(-0.56,1.40) | 0.4033 | 0.54(-0.29,1.36) | 0.2008 |
|  | Over 8 years |  |  | 0.88(0.25,1.50) | 0.0062 | 0.82(0.18,1.45) | 0.0114 |
|  |  |  |  |   |  |  |  |
| Depression | 5 years | 150, 0.15(6.03) | 157, -1.57(5.53) | 1.35(0.40,2.30) | 0.0052 | 1.06(0.27,1.86) | 0.0087 |
| (HADS-D) | 8 years | 128, 0.58(5.29) | 142, -1.44(5.72) | 1.65(0.65,2.65) | 0.0012 | 1.22(0.42,2.01) | 0.0027 |
|  | Over 8 years |  |  | 1.01(0.41,1.62) | 0.0011 | 0.85(0.26,1.44) | 0.0050 |
|  |  |  |  |   |  |  |  |
| Social function(SFQ) | 5 years | 146, 1.20(4.88) | 152, 1.27(4.56) | -0.06(-0.71,0.59) | 0.8593 | 0.22(-0.36,0.79) | 0.4633 |
|  | 8 years | 120, 1.86(4.78) | 137, 1.15(5.26) | 0.76(0.06,1.46) | 0.0333 | 0.54(-0.03,1.12) | 0.0649 |
|  | Over 8 years |  |  | 0.15(-0.22,0.52) | 0.4306 | 0.19(-0.19,0.58) | 0.3211 |
|  |  |  |  |  |  |  |  |

\* Unadjusted mixed model includes time, treatment, and time x treatment interaction as fixed effects, baseline measurement as covariate, and patient as random effect.

\*\* Unadjusted mixed model includes time, treatment, and time x treatment interaction as fixed effects, baseline measurement, clinic type, site and age as covariates, and patient as random effect.

\*\*\* Results at 3 months, 6 months, 1 year and 2 years are not reported here.

**Table 2. Summary statistics and results from mixed model analysis of clinical outcomes at 5 and 8 years: LOCF imputation**

|  |  | Summary statistics N, mean improvement from baseline (SD) | Results from mixed model analysis |
| --- | --- | --- | --- |
| Outcomes | Time\* | CBT-HA  | Standard Care  | Difference (95%CI) | P value |
|  |  |  |  |  |  |
| Health anxiety | 5 years | 219,6.19(8.64) | 225,4.19(7.53) | 2.06(0.73,3.39) | 0.0024 |
| (HAI) | 8 years | 219,6.78(8.25) | 225,4.95(7.39) | 1.89(0.56,3.22) | 0.0053 |
|  | Over 8 years |  |  | 2.53(1.48,3.59) | <.0001 |
|  |  |  |  |   |  |
| Generalized anxiety | 5 years | 219,4.65(5.72) | 225,3.80(5.34) | 0.69(-0.12,1.51) | 0.0962 |
| (HADS-A) | 8 years | 219,4.77(5.81) | 225,4.08(5.36) | 0.53(-0.29,1.34) | 0.2055 |
|  | Over 8 years |  |  | 0.81(0.18,1.44) | 0.0116 |
|  |  |  |  |   |  |
| Depression | 5 years | 219,0.51(5.64) | 225,-0.67(5.41) | 1.05(0.25,1.84) | 0.0099 |
|  | 8 years | 219,0.72(5.19) | 225,-0.61(5.47) | 1.20(0.40,1.99) | 0.0031 |
|  | Over 8 years |  |  | 0.83(0.24,1.42) | 0.0061 |
|  |  |  |  |   |  |
| Social function | 5 years | 219,1.19(4.64) | 225,1.01(4.37) | 0.21(-0.37,0.78) | 0.4813 |
|  | 8 years | 219,1.59(4.83) | 225,1.09(4.90) | 0.53(-0.04,1.11) | 0.0690 |
|  | Over 8 years |  |  | 0.19(-0.20,0.57) | 0.3422 |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

LOCF=last observation carried forward. \* Results at 3 months, 6 months, 1 year and 2 years are not reported here.

**Table 3: Summary statistics and results from mixed model analysis of clinical outcomes by therapist group at 5 and 8 years**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Summary statistics N, mean improvement from baseline (SD) | Difference between nurses and other (AP and Graduates)(95% CI), p-value\*\* |
| Outcome | Time\* |  Standard care | CBT by AP | CBT by Graduate | CBT by Nurse | ~~All~~ |
| Health anxiety (HAI) | 5 years | 158,4.34(7.75) | 65,5.21(9.17) | 42,5.55(7.91) | 42,9.29(7.72) | ~~307,5.36(8.21)~~ | 4.80(2.42, 7.18), <.0001 |
|  | 8 years | 142,5.68(7.56) | 60,5.63(7.71) | 35,6.14(8.56) | 33,10.94(5.40) | ~~270,6.37(7.66)~~ | 6.26(3.70, 8.81), <.0001 |
|  | Over 8 years |  |  |  |  |  | 4.30(2.65, 5.95) ,<.0001 |
|  |  |  |  |  |  |  |  |
| Generalized anxiety | 5 years | 158,4.54(5.48) | 66,4.94(6.27) | 42,5.95(5.50) | 42,6.14(5.02) | ~~308,5.04(5.61)~~ | 0.80(-0.67,2.28), 0.2845 |
| (HADS-A) | 8 years | 142,5.06(5.30) | 60,4.68(6.12) | 35,5.43(5.28) | 33,7.42(4.44) | ~~270,5.31(5.43)~~ | 2.67(1.07,4.28), 0.0011 |
|  | Over 8 years |  |  |  |  |  | 1.60(0.64,2.56), 0.0012 |
|  |  |  |  |  |  |  |  |
| Depression | 5 years | 157,-1.57(5.53) | 66,-0.62(5.66) | 42,-0.71(5.38) | 42,2.24(6.78) | ~~307,-0.73(5.83)~~ | 1.79(0.28,3.30), 0.0200 |
|  | 8 years | 142,-1.44(5.72) | 60,-0.43(4.99) | 35,0.43(4.48) | 33,2.58(6.14) | ~~270,-0.49(5.60)~~ | 1.75(0.10,3.40), 0.0378 |
|  | Over 8 years |  |  |  |  |  | 1.33(0.38,2.28), 0.0059 |
|  |  |  |  |  |  |  |  |
| Social function | 5 years | 152,1.27(4.56) | 66,0.53(5.41) | 42,1.07(4.10) | 38,2.50(4.55) | ~~298,1.23(4.71)~~ |  1.01(-0.05,2.08), 0.0618 |
|  | 8 years | 137,1.15(5.26) | 57,1.10(5.34) | 33,1.67(4.02) | 30,3.49(4.12) | ~~257,1.48(5.04)~~ |  1.22(0.04,2.41), 0.0425 |
|  | Over 8 years |  |  |  |  |  |  0.05(-0.53,0.64), 0.8545 |

\* Results at 3 months, 6 months, 1 year and 2 years are not reported here.

\*\* Results from mixed model which includes time, group (Standard care, Nurses, Graduates, Assistant psychologists), and time x group interaction as fixed effects, baseline measurement as covariate, and patient as random effect.

**Table 3: Summary statistics and results from mixed model analysis of clinical outcomes by therapist group at 5 and 8 years**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Summary statistics N, mean improvement from baseline (SD) | Difference between nurses and others (AP and Graduates) |
| Outcome | Time\* |  Standard care | CBT by AP | CBT by Graduate | CBT by Nurse | (95% CI), p-value\*\* |
| Health anxiety (HAI) | 5 years | 158,4.34(7.75) | 65,5.21(9.17) | 42,5.55(7.91) | 42,9.29(7.72) | 4.80(2.42, 7.18), <.0001 |
|  | 8 years | 142,5.68(7.56) | 60,5.63(7.71) | 35,6.14(8.56) | 33,10.94(5.40) | 6.26(3.70, 8.81), <.0001 |
|  | Over 8 years |  |  |  |  | 4.30(2.65, 5.95) ,<.0001 |
|  |  |  |  |  |  |  |
| Generalized anxiety | 5 years | 158,4.54(5.48) | 66,4.94(6.27) | 42,5.95(5.50) | 42,6.14(5.02) | 0.80(-0.67,2.28), 0.2845 |
| (HADS-A) | 8 years | 142,5.06(5.30) | 60,4.68(6.12) | 35,5.43(5.28) | 33,7.42(4.44) | 2.67(1.07,4.28), 0.0011 |
|  | Over 8 years |  |  |  |  | 1.60(0.64,2.56), 0.0012 |
|  |  |  |  |  |  |  |
| Depression | 5 years | 157,-1.57(5.53) | 66,-0.62(5.66) | 42,-0.71(5.38) | 42,2.24(6.78) | 1.79(0.28,3.30), 0.0200 |
|  | 8 years | 142,-1.44(5.72) | 60,-0.43(4.99) | 35,0.43(4.48) | 33,2.58(6.14) | 1.75(0.10,3.40), 0.0378 |
|  | Over 8 years |  |  |  |  | 1.33(0.38,2.28), 0.0059 |
|  |  |  |  |  |  |  |
| Social function | 5 years | 152,1.27(4.56) | 66,0.53(5.41) | 42,1.07(4.10) | 38,2.50(4.55) | 1.01(-0.05,2.08), 0.0618 |
|  | 8 years | 137,1.15(5.26) | 57,1.10(5.34) | 33,1.67(4.02) | 30,3.49(4.12) | 1.22(0.04,2.41), 0.0425 |
|  | Over 8 years |  |  |  |  | 0.05(-0.53,0.64), 0.8545 |
|  |  |  |  |  |  |  |

\* Results at 3 months, 6 months, 1 year and 2 years are not reported here.

\*\* Results from mixed model which includes time, group (Standard care, Nurses, Graduates, Assistant Psychologists (AP)), and time x group interaction as fixed effects, baseline measurement as covariate, and patient as random effect.

Table 4: Summary results from mixed model analysis of HAI change from baseline at 8 years: Subgroup analysis

|  | Summary statistics N, mean improvement from baseline (SD |
| --- | --- |
| Variable | Subgroup | CBT | TAU | Difference (95%CI) | P-value |
| Age group | <=49 | 63,6.68(8.36) | 79,5.69(7.06) | 2.72(1.04,4.40) | 0.0015 |
|  | >49 | 86,6.28(8.76) | 79,2.98(8.21) | 2.56(1.16,3.95) | 0.0003 |
| Clinic | Cardiology | 33,8.73(7.93) | 38,3.56(8.62) | 4.17(1.98,6.37) | 0.0002 |
|  | Endocrinology | 28,4.89(6.82) | 30,3.70(6.30) | 1.09(-1.37,3.54) | 0.3846 |
|  | Gastroenterology | 57,5.77(9.02) | 55,4.78(7.73) | 2.57(0.70,4.44) | 0.0073 |
|  | Neurology | 13,9.08(9.05) | 17,5.53(8.19) | 2.67(-0.87,6.21) | 0.1382 |
|  | Respiratory Medicine | 18,4.97(9.87) | 18,4.53(8.27) | 1.26(-1.68,4.21) | 0.3983 |

Table 4: Summary results from mixed model analysis of HAI change from baseline at 8 years: Subgroup analysis

|  |  | Summary statistics N, mean improvement from baseline (SD | Results from mixed model analysis |
| --- | --- | --- | --- |
| Variable | Subgroup | CBT | TAU | Difference (95%CI) | P-value |
| Age group | <=49 | 63,6.68(8.36) | 79,5.69(7.06) | 2.72(1.04,4.40) | 0.0015 |
|  | >49 | 86,6.28(8.76) | 79,2.98(8.21) | 2.56(1.16,3.95) | 0.0003 |
| Clinic | Cardiology | 33,8.73(7.93) | 38,3.56(8.62) | 4.17(1.98,6.37) | 0.0002 |
|  | Endocrinology | 28,4.89(6.82) | 30,3.70(6.30) | 1.09(-1.37,3.54) | 0.3846 |
|  | Gastroenterology | 57,5.77(9.02) | 55,4.78(7.73) | 2.57(0.70,4.44) | 0.0073 |
|  | Neurology | 13,9.08(9.05) | 17,5.53(8.19) | 2.67(-0.87,6.21) | 0.1382 |
|  | Respiratory Medicine | 18,4.97(9.87) | 18,4.53(8.27) | 1.26(-1.68,4.21) | 0.3983 |