

# A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale

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Accepted for publication 9 August 2011

Study Type – Therapy (RCT)  
Level of Evidence 1b

## OBJECTIVE

- To evaluate the effect of i.m. injection of testosterone undecanoate 1000 mg over 12 months on the Aging Male Symptom (AMS) scale scores in men with testosterone deficiency syndrome (TDS).

## PATIENTS AND METHODS

- A total of 120 men >40 years old with TDS (total testosterone < 12 nmol/L and total AMS scores ≥ 27) were randomized into i.m. injection of either placebo or testosterone undecanoate 1000 mg.
- In all, 56 and 58 participants from the active treatment and placebo groups, respectively completed the study.
- An i.m. injection of either placebo or testosterone undecanoate 1000 mg was given at weeks 0, 6, 18, 30 and 48.
- Self-administered AMS questionnaires were completed at weeks 0, week 18 and week 48.

## What's known on the subject? and What does the study add?

Testosterone deficiency syndrome can be treated with testosterone replacement in the form of injectable, transdermal, buccal and oral preparations. Long-acting i.m. testosterone undecanoate 1000 mg, which is given at 10–14 week intervals, has been shown to be adequate for sustaining normal testosterone levels in hypogonadal men.

This study confirms that long-acting i.m. testosterone undecanoate is effective in improving the health-related quality of life in men with testosterone deficiency syndrome as assessed by the improvement in the Aging Male Symptoms scale. Testosterone treatment can be indicated in men who have poor health-related quality of life resulting from testosterone deficiency syndrome.

## RESULTS

- Improvement in the total AMS score was significantly greater in the treatment group than in the placebo group (F: 4.576,  $P = 0.017$ ) over the 48-week period.
- The mean (SD) total AMS score was 38.46 (11.85) at baseline and 33.59 (1.69) at 48 weeks for the placebo group, and 41.73 (12.73) at baseline and 32.61 (9.67) at 48 weeks for the treatment group.
- The mean change in the total AMS score was –12.6% in the placebo group and –21.9% in the treatment group.
- The mean psychological and somatovegetative domain scores decreased significantly more in the treatment group

than in the placebo group (–2.8 vs –1.2,  $P = 0.03$ ; and –3.2 vs –1.8,  $P = 0.016$ ).

- The difference in change between the randomized groups for the sexual domain scores followed the same trend, though the difference was not significant.

## CONCLUSION

- Long-acting testosterone is effective in improving health-related quality of life as assessed by the AMS scale in men with TDS.

## KEYWORDS

testosterone deficiency, hypogonadism, testosterone undecanoate, injectable, long-acting, AMS scale

## INTRODUCTION

Men's health has become a key concern and challenge for healthcare professionals and policy makers. Amongst the most prominent

healthcare issues of the 21<sup>st</sup> century are those related to aging and, with regard to men's health, the aging male. Worldwide, the elderly population is growing faster than any other age group. Observational studies

have reported that there is a consistent decline in total testosterone levels at a rate of 1–2% per year starting from a man's late 30 s [1]. Testosterone deficiency syndrome (TDS) in adult males is associated with

numerous physical, psychological and sexual symptoms. Testosterone replacement therapy has been shown to improve symptoms as well as health-related quality of life (HRQoL) related to TDS [2,3].

There are many tools for the measurement of HRQoL in hypogonadal men. These include the Aging Male Symptom (AMS) scale, the WHO quality-of-life scale, the 12- and 36-item short-form health surveys, and the androgen deficiency in adult males (ADAM) scale. The AMS scale was originally developed in Germany in 1991 [4], with the aim of assessing aging symptoms among groups of males under different conditions, evaluating the severity of symptoms over time, and measuring changes before and after androgen replacement therapy [5]. The development of the AMS scale at that time was in response to the lack of fully standardized scales to measure the severity of aging symptoms and their impact on HRQoL in males, specifically [6,7].

Many studies have shown that the AMS scale correlates with testosterone levels and predicts hypogonadism [8–13]. It also meets the requirements of clinical utility and outcomes sensitivity [8]. Heinemann *et al.* [8] have also convincingly shown that the AMS scale has the ability to measure treatment effects on HRQoL across the full range of severity of complaints. In addition, the results of the AMS scale can predict subjective clinical expert opinion on treatment efficiency [14]. Weak correlations were also reported between AMS scale domain scores (psychological, somatic and sexual) and testosterone levels [9,10].

There are very few studies reporting the effect of testosterone therapy using the AMS scale. In one of the largest placebo-controlled studies of testosterone therapy in late-onset hypogonadism, it was found that the effect of oral testosterone undecanoate (Andriol Testocaps™, Merck, Sharp and Dohme, Whitehouse Station, NJ, USA) on total AMS scores during 12 months of treatment was not significantly different from placebo, except for sexual symptoms, where a modest improvement was reported with oral testosterone undecanoate 160 mg/day [15]. In a study by Moore *et al.* [16] on an injectable testosterone enanthate product (Testosterone-Depot, Jenapharm, Jena, Germany), it was found that the increased mean total AMS score at baseline (before

treatment) decreased after 12 weeks of treatment, indicating a significant improvement in symptoms and in HRQoL. These authors also showed that AMS scale scores can predict subjective clinical expert opinion on the efficacy of the treatment.

Recently, a new preparation of long-acting injectable testosterone undecanoate (Nebido®, Bayer Schering, Leverkusen, Germany) has been brought onto the market. This undecanoate ester formulation of testosterone with castor oil, extends the maximum dosing interval by about fourfold compared with that of other injectable formulations of testosterone [17]. Studies in Europe have reported that 1000 mg testosterone undecanoate as an i.m. injection at 10–14-week intervals is adequate for sustaining normal testosterone levels in hypogonadal men [18]. Similar findings were found in studies done in Asia and Australia.

The objective of the present study was to investigate the effect of i.m. injection of testosterone undecanoate 1000 mg over 12 months on the AMS scores for Malaysian men with low serum testosterone levels.

## PATIENTS AND METHODS

### STUDY DESIGN

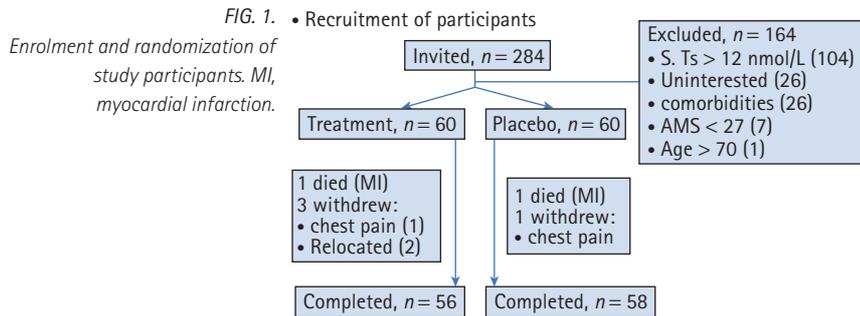
The present study was a double-blind, parallel, randomized, placebo-controlled trial with an allocation ratio of 1:1. It was approved by the Medical Ethics Committee, University of Malaya Medical Centre (approval number: 631.11) and was conducted in accordance with the ethical principles of the Malaysian Good Clinical Practice Guidelines that are based on the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. The primary endpoint of the present study was treatment effect on AMS scores. The secondary endpoints were adverse events, anthropometric changes and changes in laboratory blood results, i.e. fasting lipid, fasting blood glucose, liver function tests, total testosterone and serum hormone binding globulin levels, and International Prostate Symptoms Score (IPSS) and 12-item short-form health survey (SF-12) questionnaire results.

### RESEARCH TOOL

We used the AMS scale, which measures severity of subjectively perceived complaints in each of the 17 items on a scale of 1–5, a higher score meaning greater symptom severity [16]. The composite scores for each of the domains is based on adding up the scores of the items of the respective domains. The composite score (total score) is the sum of the domain scores. The cumulative score can range from 17 to 85 points. The severity of the symptoms are defined as: no/low (17–26 points), mild (27–36 points), moderate (37–49 points) and severe ( $\geq 50$  points). The three domains of the AMS scale are psychological, somatovegetative and sexual. Heinemann *et al.* [6] translated the original German AMS scale into the culturally adapted English-language scale and showed that there was cross-cultural equivalence.

### SUBJECTS

Participants were recruited by phone-call invitation to form a cohort of randomly selected men aged  $\geq 40$  years from an urban community. Participants, who gave written informed consent to participate, underwent initial screening tests which included an early morning total testosterone test and the completion of the AMS questionnaire. If the participant's total testosterone level was  $< 12$  nmol/L and total AMS score was  $\geq 27$  (corresponding to mild to severe symptoms of TDS), he was called back for a formal screening visit to establish whether he fulfilled the study criteria. The inclusion criteria were: age 40–70 years; having at least 'mild' symptoms for all three AMS domains (scores of  $\geq 9$  in the somatovegetative,  $\geq 6$  in the psychological and  $\geq 6$  in the sexual domain) or total AMS scores  $\geq 27$ ; having early morning total testosterone level  $< 12$  nmol/L on two occasions; and a PSA level of  $< 4$  ng/mL. The exclusion criteria were: uncontrolled diabetes mellitus (HbA1c  $> 8\%$ ); clinical hypothyroidism or hyperthyroidism; haematocrit  $> 55\%$ ; known prostate cancer; androgen-dependent carcinoma of the male mammary gland; past or present liver tumours; other significant medical conditions (American Society of Anaesthetists score  $> 3$ ) or psychological conditions (psychosis, schizophrenia or manic depression); or clinically diagnosed sleep apnoea. Participants were also



excluded if they were on medication known to interfere with testosterone metabolism, had hypersensitivity to the active substance or excipients of the study medication, testosterone treatment (transdermal, oral or i.m.) within the previous 6 months or testosterone implants within the previous 12 months.

#### SAMPLE SIZE

The sample size was calculated based on the improvement in AMS score, the primary endpoint of the study. With a two-sided  $\alpha$  value of 0.05 and a power of 80%, a sample size of 60 subjects per arm would be able to detect a 4.64 reduction in the AMS scores from the baseline (30.8) at 48 weeks after intervention with a population sd of 8.98 [19]. This sample size would be able to detect a minimum point difference of 8.78 in HRQoL score with an estimated population sd of 17 [20].

#### STUDY PROTOCOL

The study was conducted at a tertiary medical centre in Malaysia. All participants who fulfilled the study criteria were assessed by clinical investigators (certified medical doctors) to establish their baseline profiles, which included a physical assessment of their weight, height, blood pressure and prostate (by DRE), a recording of current medications and concurrent illnesses, recording biochemistry profiles (total testosterone, haematocrit and serum PSA levels and liver function test results) and recording their IPSS, and AMS scale and SF-12 questionnaire scores.

After reviewing the baseline assessment results, each participant received an intervention package indexed with a serial number at visit 1. Each package contained five vials of either all placebo or active

medication, prepared in an identical form. Each serial number with its code for either placebo or active medication was kept in a sealed envelope. The supplier of the intervention packages and the envelopes was not involved in any stage of the trial. Hence, the participants, clinical investigators and trial site manager were all blinded to the types of intervention until the trial period was over, when only then, the codes were revealed. Revealing the codes within the trial period was permitted only when there was an occurrence of serious adverse event.

Repeat physical assessments (except DRE) were done for every encounter with participants, at weeks 6, 18, 30, 42 and 48 after the first intervention. Serum total testosterone and biochemistry profiles were repeated at weeks 18 and 48; DRE, administration of IPSS, AMS and SF-12 questionnaires was done at weeks 18 and 48. The serum testosterone results were not revealed to participants or investigators until the trial period was over. All laboratory investigation was carried out by a single laboratory to maintain standardization of measurement and reference points.

#### INTERVENTION

All participants received five injections from the package allocated to them at weeks 0, 6, 18, 30 and 42 after formal enrolment. The active treatment was 1000 mg of testosterone undecanoate in 4 mL of castor oil, and placebo was just castor oil of the same volume and appearance. The injection was given as slow bolus i.m. at the gluteal region over 1 min.

#### OUTCOME MEASUREMENTS

The primary endpoint was the improvement in symptoms and HRQoL from baseline to

48 weeks as measured by the total AMS score (at screening, 18 and 48 weeks) and individual domain scores. The secondary endpoints were adverse events, anthropometric changes, laboratory blood results, and IPSS and SF-12 scores. The secondary endpoints will be reported in a separate paper.

#### SAFETY MONITORING AND WITHDRAWAL

Participants' safety was monitored by scheduled assessment and self-reporting of adverse events. Scheduled assessment included a clinical assessment (with a repeat DRE at week 30) for every visit and monitoring of biochemistry profiles at weeks 18 and 48. Every participant was asked to report any symptom after commencement of the intervention. Mandatory reviews and consideration for withdrawal from the study were undertaken if any of the following criteria were noted: a rise in PSA level of  $\geq 50\%$  from the baseline or to  $>4$  ng/mL, any clinical abnormality on DRE, a significant worsening of IPSS, a rise in haematocrit of  $>55\%$  or any report of adverse event.

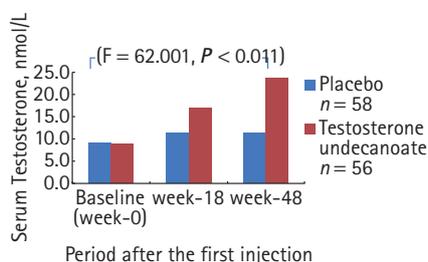
#### STATISTICAL ANALYSES

Descriptive statistics were used for baseline demographics, outcome measurements and adverse events. In comparing the baseline profiles and adverse events between the active treatment and placebo groups, exact contingency table methods were used for categorical data, and an independent sample *t*-test was used for continuous data. Responses to outcome measures for each group were calculated as the difference from their baseline values. The effects of active treatment on HRQoL scores were estimated using repeated measure ANOVA by including the intervention  $\times$  time interaction terms. The two-sided level of significance (*P*) was set at 0.05. Data analysis was done using the Statistical Package for the Social Sciences (SPSS Inc., Chicago IL, USA) version 15.

#### RESULTS

The present study was carried out between May 2008 and February 2010. A total of 284 men were invited to participate in the study (Fig. 1). After excluding 164 men, 120 men were recruited and randomized equally into the treatment and placebo groups, but only

FIG. 2. Comparison of serum testosterone levels in the testosterone undecanoate group vs the placebo group from baseline to week 48 using repeated measure ANOVA.



56 participants in the treatment and 58 in the placebo group completed the study. In the treatment group, one patient died from myocardial infarction while three withdrew from the study (one because of chest pain and another two because of relocation to another state). In the placebo group, one patient died from myocardial infarction and another withdrew because of chest pain. The two patients who withdrew because of myocardial infarction had a history of ischaemic heart disease. The other two who withdrew because of chest pain refused further investigation.

Table 1 shows the baseline characteristics of the treatment and placebo groups. Despite the randomization there were significant differences between the two groups in the following: body mass index, waist circumference, diastolic blood pressure, total AMS score and the AMS psychological domain score.

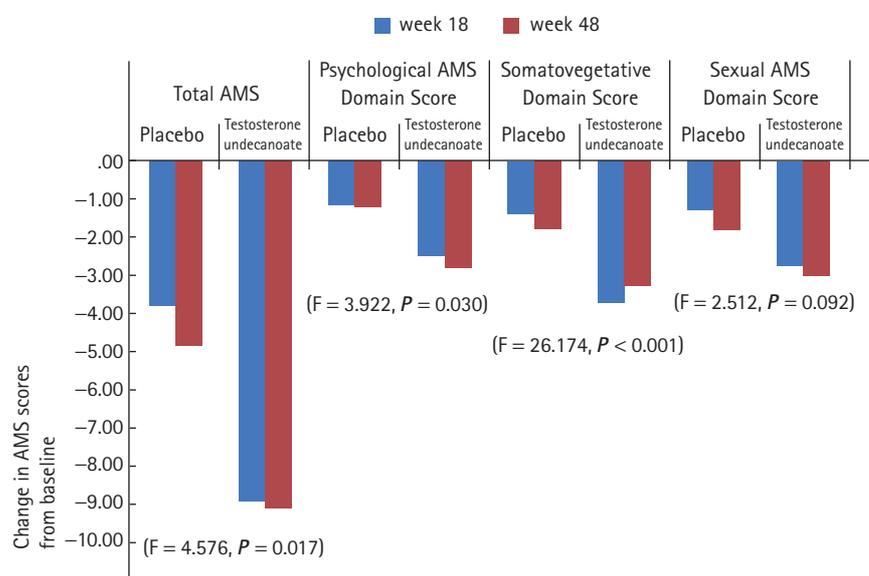
The participants' mean (sd) age was 53.4 (7.4) years in the treatment group and 53.0 (8.2) years in the placebo group. At 48 weeks, administration of testosterone undecanoate 1000 mg significantly increased mean serum testosterone levels from 8.9 to 23.8 nmol/L compared with placebo, which increased them from 9.1 to 11.2 nmol/L ( $F = 62.001$ ,  $df = 2.000$ ,  $P < 0.001$  [Fig. 2]).

The improvement in the total AMS score was significantly greater in the treatment arm compared with the placebo arm ( $F = 4.576$ ,  $df = 2.000$ ,  $P = 0.017$ ) over the 48-week period (Fig. 3). The change in mean total AMS score was  $-12.6\%$  in the placebo group and  $-21.9\%$  in the testosterone undecanoate 1000 mg group. Similarly, over

TABLE 1 Baseline characteristics of the placebo and testosterone undecanoate groups

	Placebo	Testosterone undecanoate
Mean (SD) body mass index, kg/m <sup>2</sup>	28.2 (4.5)	30.4 (5.2)
Mean (SD) waist circumference, cm	96.3 (10.7)	102.7 (12.3)
Mean (SD) systolic blood pressure, mmHg	127.9 (10.4)	132.5 (14.6)
Mean (SD) diastolic blood pressure, mmHg	81.4 (6.4)	84.1 (7.4)
Mean (SD) total testosterone level (nmol/L)	9.1 (1.8)	8.9 (2)
Mean (SD) serum hormone binding globulin level, nmol/L	20.9 (6.9)	21.6 (7)
Mean (SD) total AMS score	38.2 (11.9)	42.9 (13.2)
somatic subscale	15.8 (5.4)	17.6 (5.6)
psychological subscale	10.0 (4.0)	11.6 (4.5)
sexual subscale	12.4 (4.3)	13.7 (4.4)
Ethnicity, n (%)		
Malay	15 (25.0)	16 (26.7)
Chinese	25 (41.7)	25 (41.7)
Indian	17 (28.3)	17 (28.3)
Others	3 (5.0)	2 (3.3)
Comorbidities, n (%)		
Hypertension	20 (33.3)	29 (48.3)
Diabetes mellitus	9 (15.0)	14 (23.3)
Dyslipidemia	20 (33.3)	22 (36.7)
Coronary artery disease	3 (5.0)	6 (10.0)

FIG. 3. Comparison of changes in the total AMS and domain scores in the testosterone undecanoate group vs the placebo group.



the 48-week period, the mean AMS psychological and somatovegetative domain scores decreased significantly more in the testosterone undecanoate 1000 mg arm than in the placebo arm ( $-2.8$  vs  $-1.2$ ,  $P = 0.03$  and  $-3.2$  vs  $-1.8$ ,  $P = 0.016$ , respectively), but there was no significant

difference in the change in sexual subscale scores between the two groups (Table 2).

## DISCUSSION

The present study showed that long-acting testosterone undecanoate treatment

TABLE 2 Comparison of total AMS scores and AMS domain scores of the placebo and testosterone undecanoate groups

AMS score	Intervention group	Baseline	Week 18	Week 48	Repeated measure	
					ANOVA, F	P
Mean (SD) total AMS sum score	Placebo	38.46 (11.85)	34.66 (10.06)	33.59 (10.69)	4.576	0.017
	Testosterone undecanoate	41.73 (12.73)	32.73 (9.71)	32.61 (9.67)		
Mean (SD) psychological domain score	Placebo	10.03 (3.98)	8.88 (3.38)	8.81 (3.30)	3.922	0.03
	Testosterone undecanoate	11.11 (4.30)	8.61 (3.41)	8.27 (3.05)		
Mean (SD) somatovegetative domain score	Placebo	15.93 (5.34)	14.58 (4.58)	14.12 (5.05)	26.174	<0.001
	Testosterone undecanoate	17.18 (5.52)	13.43 (4.67)	13.89 (4.48)		
Mean (SD) sexual domain score	Placebo	12.49 (4.29)	11.20 (3.42)	10.66 (3.95)	2.512	0.092
	Testosterone undecanoate	13.45 (4.34)	10.70 (3.63)	10.45 (3.69)		

significantly improved total AMS scores. On analysis of the AMS domain scores, we found that the psychological and somatovegetative scores also improved significantly with treatment. The sexual domain scores also improved with testosterone undecanoate treatment but the improvement was not significant. Cultural factors could have influenced the outcome as the AMS questionnaire could have been interpreted differently by the Malaysian population in the present study as compared to a Western population.

The present findings concurred with four other studies from Korea, Russia, Italy and Thailand, which included the assessment of AMS score after treatment with testosterone undecanoate.

In the Korean study [3], the main aim was to assess the efficacy and safety of long-acting injectable testosterone undecanoate. Secondary efficacy was measured using AMS scores. The participants' characteristics were similar to those in the present study; participants were Asian and their mean (SD) age was 54 (9.6) years. In the Korean study, however, if the treating physician felt that there was no clinical improvement in erectile function within 18 weeks of the treatment period, phosphodiesterase-5 inhibitor medication (vardenafil 20 mg) was used along with testosterone replacement therapy from the 18th week to the end of the follow-up period. As a result, 17 patients were prescribed concomitant phosphodiesterase-5 inhibitor medication from 18–24 weeks. This could have improved the AMS sexual domain score significantly compared with the present results, which showed a nonsignificant

improvement in the AMS sexual domain score. Another difference to note is that the present study was a randomized controlled trial comparing testosterone undecanoate against placebo. We also assessed the AMS score over a longer period of time (48 weeks) than the authors of the Korean study (24 weeks).

The Russian study was a randomized, placebo-controlled trial assessing the effects of testosterone supplementation on depressive symptoms and sexual dysfunction in men with both hypogonadism and metabolic syndrome [21]. Similarly to the present study, the testosterone undecanoate group had slightly higher AMS scores at baseline but the difference was not significant. In the present study, the difference was significant. In the Russian study, as compared with placebo, there were improvements in total AMS score over time. The time x group effect was largely negligible after adjustment for age, and baseline body mass index, smoking status, total testosterone level, and prevalent diabetes mellitus. The AMS subscale scores were not analysed.

The Italian study was a randomized, double-blind, double-dummy study that investigated the efficacy and safety of oral and i.m. testosterone undecanoate in hypogonadal men with metabolic syndrome [22]. Only 32 men were randomized to receive i.m. testosterone undecanoate. In contrast to the present study, there was significant improvement in the sexual domain subscores with i.m. testosterone undecanoate at 6 and 12 months. The present study also showed an improvement in this domain but this was not significant.

The interesting thing to note in the Italian study was that those on oral testosterone undecanoate for 6 months did not show significant changes in all AMS scores, but when they switched to the i.m. preparation, the total and somatovegetative domain scores improved significantly. The sexual and psychological domain score changes were not significant, although the sexual domain score did show an improvement.

In the study from Thailand, the scores of all domains of the AMS questionnaire decreased with i.m. testosterone undecanoate but only the psychological domain score improvement was significant ( $P = 0.044$ ) [23]. The improvement in the sexual and somatovegetative domain scores were not significant ( $P = 0.200$  and  $P = 0.071$ , respectively). The present study, however, was not a randomized prospective trial.

In the present study, adverse coronary events were noted but at the beginning of the study period, no adverse coronary events after treatment with testosterone were reported in the literature. A history of ischaemic heart disease was, therefore, not one of our exclusion criteria. Basaria *et al.* [24] reported the adverse coronary events associated with testosterone only in July 2010, after our study had concluded. Needless to say, the present study adds to the evidence that adverse coronary events are associated with testosterone.

In conclusion, long-acting testosterone is effective in improving the HRQoL in men with TDS as assessed by improvement in AMS scale scores. Testosterone treatment

can be indicated in men who have poor HRQoL resulting from TDS.

## CONFLICT OF INTEREST

None declared. This study was supported financially by Bayer Schering Pharma.

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**Abbreviations:** AMS, Aging Male Symptoms; TDS, testosterone deficiency syndrome; HRQoL, health-related quality of life; SF-12, 12-item short-form health survey.