

Is Subclinical Thyroid Dysfunction in the Elderly Associated with Depression or Cognitive Dysfunction?

Lesley M. Roberts, PhD; Helen Pattison, PhD; Andrea Roalfe, MSc; Jayne Franklyn, MD, PhD; Sue Wilson, PhD; F.D. Richard Hobbs, MB ChB; and James V. Parle, MD

Background: Widespread use of automated sensitive assays for thyroid hormones and thyroid-stimulating hormone (TSH) has increased identification of mild thyroid dysfunction, especially in elderly patients. The clinical significance of this dysfunction, however, remains uncertain, and associations with cognitive impairment, depression, and anxiety are unconfirmed.

Objective: To determine the association between mild thyroid dysfunction and cognition, depression, and anxiety in elderly persons.

Design: Cross-sectional study. Associations were explored through mixed-model analyses.

Setting: Primary care practices in central England.

Patients: 5865 patients 65 years of age or older with no known thyroid disease who were recruited from primary care registers.

Measurements: Serum TSH and free thyroxine (T_4) were measured. Depression and anxiety were assessed by using the Hospital Anxiety and Depression Scale (HADS), and cognitive functioning was established by using the Middlesex Elderly Assessment of Mental State and the Folstein Mini-Mental State Examination. Comorbid conditions, medication use, and sociodemographic profiles were recorded.

Results: 295 patients met the criteria for subclinical thyroid dysfunction (127 were hyperthyroid, and 168 were hypothyroid). After confounding variables were controlled for, statistically significant associations were seen between anxiety (HADS score) and TSH level ($P = 0.013$) and between cognition and both TSH and free T_4 levels. The magnitude of these associations lacked clinical relevance: A 50-mIU/L increase in the TSH level was associated with a 1-point reduction in the HADS anxiety score, and a 1-point increase in the Mini-Mental State Examination score was associated with an increase of 50 mIU/L in the TSH level or 25 pmol/L in the free T_4 level.

Limitations: Because of the low participation rate, low prevalence of subclinical thyroid dysfunction, and other unidentified recruitment biases, participants may not be representative of the elderly population.

Conclusions: After the confounding effects of comorbid conditions and use of medication were controlled for, subclinical thyroid dysfunction was not associated with depression, anxiety, or cognition.

Ann Intern Med. 2006;145:573-581.

For author affiliations, see end of text.

www.annals.org

The advent of automated sensitive assays for thyroid hormones and thyroid-stimulating hormone (TSH) and the increasingly widespread use of such tests have led to a substantial increase in the identification of mild thyroid dysfunction, especially in elderly patients. This, in turn, has led many physicians to treat subclinical (also known as “mild”) dysfunction. However, the clinical significance of mild thyroid dysfunction remains uncertain, and evidence on the efficacy or safety of treatment is limited (1–3).

Subclinical thyroid dysfunction is characterized by an abnormal serum level of TSH in association with normal serum levels of thyroid hormone. Subclinical hypothyroidism is defined biochemically as an increased serum TSH level with a normal serum free thyroxine (T_4) level, and subclinical hyperthyroidism as a decreased serum TSH level with normal levels of free T_4 and free triiodothyronine.

One postulated consequence of minor abnormalities of thyroid function, especially subclinical hypothyroidism, is an effect on cognitive functioning and mood. The association between overt hypothyroidism and cognitive dysfunction is well established (4, 5), although more recent evidence suggests that this association is confounded by mood (6). Whether a similar association exists with mild or subclinical hypothyroidism is uncertain.

Some studies report no association between subclinical

hypothyroidism and measures of cognition (5, 7–9), whereas others have identified between-group differences in cognitive functioning when patients with subclinical hypothyroidism were compared with euthyroid controls (10). A recent study (11) with a case-matched design demonstrated no differences in cognitive functioning between subclinically hypothyroid and euthyroid patients, although the criteria for defining subclinical hypothyroidism were atypical (an upper TSH limit of 3.5 mIU/L) and external validity was reduced by the exclusion of patients with serious illness or a history of cardiovascular disease.

Associations between subclinical hypothyroidism and depression have also been described (6, 10, 12, 13), but many of these studies were based on small samples and were subject to selection and recruitment bias. An associa-

See also:

Print

Editors' Notes 574
Summary for Patients I-52

Web-Only

Appendix Figure
Conversion of figure and tables into slides

Context

The relationship between subclinical thyroid dysfunction and disorders of cognition and mood is unclear.

Contribution

The authors studied 5868 general practice patients 65 years of age or older with a detailed medical history, thyroid tests, and standardized tests of cognition and mood. They found no association between subclinical thyroid dysfunction and anxiety, depression, or cognitive impairment in prediction models that adjusted for age, sex, social deprivation, medications, and comorbid diseases.

Implications

This study provides good evidence that subclinical thyroid dysfunction is not related to disorders of cognition and mood in older persons.

—The Editors

tion between subclinical dysfunction and anxiety has also been demonstrated (14). Nevertheless, the largest reported study to date (30 589 patients) (15) showed no association between subclinical hypothyroidism and depression or anxiety, findings that have been reported elsewhere (9, 11).

A recent systematic review that aimed to determine any association between thyroid dysfunction and cognitive function and mood concluded that evidence is insufficient to confirm or refute an association with subclinical hypothyroidism or subclinical hyperthyroidism (1). We used standard diagnostic criteria to examine these possible associations in a large community-based cohort of persons 65 years of age or older (the Birmingham Elderly Thyroid Study). We recorded measures of thyroid function, cognitive functioning, depression, and anxiety and report on associations after controlling for the confounding effects of comorbid illness and medication use.

METHODS**Recruitment and Participants**

Participants were recruited from 20 primary care practices in central England. The sample was selected to encompass patients from a range of socioeconomic backgrounds. To maximize generalizability to the primary care population, all patients who did not have an active diagnosis of thyroid disease were included. Patients were excluded if they had received antithyroid treatment within the previous 12 months or were currently receiving treatment for a thyroid disorder, or if their family physician deemed that contact was inappropriate (for example, because of recent bereavement or inability to give informed consent). All other patients 65 years of age or older were eligible and were invited to participate by letter. Because the uptake rate was only 14.6% among the first 699 patients older than 85 years of age who were contacted, re-

cruitment was subsequently limited to patients 65 to 84 years of age (inclusive) for the remainder of the study, although previously contacted patients who were older than 84 years of age remained eligible. Patients who accepted the invitation received an appointment with a research or trained primary care nurse at their usual primary care practice or their home.

Ethical approval was obtained from the Multi-Centre Research Ethics Committee (Scotland), and local approval was confirmed before commencement of the study. Written informed consent was obtained from all participants.

Measurements and Sample Size

Patients were placed under no restrictions on eating or medication use before serum samples were obtained for testing. Serum samples were obtained during normal office hours and were treated and collected according to the practice's usual procedure for blood collection. Serum TSH and free T₄ were measured by using a chemiluminescent immunoassay (Adiva Centaur [Bayer Diagnostics, Newbury, United Kingdom]) in the Regional Endocrine Laboratory of the University Hospital Birmingham National Health Service Trust. Interassay coefficients of variation were 4.4% to 10.9% over 0.41 to 24.5 mIU/L for the TSH assay and 8.2% to 9.8% over 8.2 to 54.9 pmol/L for the free T₄ assay. The laboratory reference range was 0.4 to 5.5 mIU/L for TSH and 9.0 to 20.0 pmol/L for free T₄. Serum free triiodothyronine was measured by chemiluminescent assay (Avida Centaur) in all cases in which the TSH level was less than 0.4 mIU/L or a within-range TSH level was accompanied by an elevated free T₄ level. The reference range for the triiodothyronine assay was 3.5 to 6.5 pmol/L, and the interassay coefficient of variation was 4.2% to 6.9% over 4.0 to 16.0 pmol/L.

The Index of Multiple Deprivation 2004 (16) was calculated for each participant on the basis of his or her postal code. This proxy measure of socioeconomic deprivation encompasses 7 domains: income; employment; health and disability; education, skills, and training; barriers to housing and services; living environment; and crime. All major current or previous medical diagnoses and current drug therapies were recorded on the basis of patient reporting and validation from primary care records. Diagnoses were categorized in line with recognized disease groupings. Medications that are known to interact with thyroid function, anxiety, depression, or cognition were coded under generic headings.

Cognition was assessed by using the Folstein Mini-Mental State Examination (MMSE) (17), which is widely used to determine cognitive status in clinical and research settings, and the Middlesex Elderly Assessment of Mental State (MEAMS) (18), which was developed as a screening test to detect gross impairment of specific cognitive skills in elderly persons and systematically surveys the major areas of cognitive performance. Aspects covered by MEAMS include orientation, learning, memory, numeracy, percep-

Table 1. Values Used to Categorize Thyroid Status

Thyroid Status	Thyroid-Stimulating Hormone Level, mIU/L	Free Thyroxine Level, pmol/L*	Free Triiodothyronine Level, pmol/L†	Participants, n
Overt hyperthyroidism	<0.4	9.0–20.0	>6.5	4
	<0.4	>20.0	>6.5	11
Subclinical hyperthyroidism	<0.4	<9.0	≥3.5	0
	<0.4	9.0–20.0	≤6.5	127
Euthyroidism				
Quartile 1	0.4–1.10			1471
Quartile 2	1.11–1.60			1428
Quartile 3	1.61–2.30			1314
Quartile 4	2.31–5.50			1311
Subclinical hypothyroidism	>5.5	9.0–20.0		168
Overt hypothyroidism	>5.5	<9.0		23
Uncategorizable	<0.4	<9.0	<3.5	1
	<0.4	>20.0	≤6.5	10

*Laboratory reference range, 9.0 to 20.0 pmol/L.

† Laboratory reference range, 3.5 to 6.5 pmol/L.

tion, attention, and language skills. Both tests comprise a range of tasks that all elderly persons without cognitive impairment should be able to complete, regardless of intelligence. Possible scores on the MMSE range from 0 to 30. Subtests in MEAMS can be used alone, or a combined score can be produced (range, 0 to 12). In both tests, higher scores indicate less dysfunction. Nurses were trained in the administration of all tests to the required standard.

Symptoms of depression and anxiety were self-reported by using the Hospital Anxiety and Depression Scale (HADS) (19), which consists of 7 items for depression and 7 for anxiety. Each item is scored from 0 to 3, and the maximum total score on each scale is 21. Scores of 8 to 10 indicate mild disorder, scores of 11 to 14 indicate moderate disorder, and scores of 15 or greater indicate severe anxiety or depression.

Assuming a prevalence of 9% for subclinical hypothyroidism and 6% for subclinical hyperthyroidism, a planned sample size of 6200 patients was sufficient to detect a difference between the subclinical and euthyroid groups of 0.4 unit (SD, 2.2) in MMSE score (20) and 0.7 unit (SD, 3.6) in HADS score (21), with 90% power and 5% significance.

Data Management and Coding

Participants were classified according to serum free thyroid hormone and TSH levels into 1 of 5 categories: overt hypothyroidism, subclinical hypothyroidism, euthyroidism, subclinical hyperthyroidism, and overt hyperthyroidism. Euthyroidism was further subdivided into quartiles before analysis. Participants who could not be categorized on the basis of thyroid function results were excluded from analyses. Table 1 shows details of criteria for classification.

In cases where only 1 item per scale was missing on the HADS data, the missing value was imputed by using mean scores. Missing values on MEAMS and MMSE were not imputed because of the heterogeneity of individual tests

(which measured distinct aspects of cognitive processing) and the fact that some processes are assessed by only 1 or 2 items. Participants for whom data were incomplete were excluded from corresponding analyses.

Statistical Analysis

Analyses were done by using SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina). Associations between thyroid status as a categorical variable and cognition, anxiety, and depression scores were investigated by using mixed-model analyses. Pairwise comparisons of adjusted means for thyroid categories were made within the mixed-model analysis. Five models were performed for each outcome. Model 1 was an unadjusted model that included thyroid status only; model 2 incorporated model 1 plus age, sex, and practice; model 3 included model 2 plus deprivation; model 4 included model 3 plus specified comorbid conditions; and model 5 included model 4 plus specified medications. Comorbid conditions were aortic stenosis, cancer, cerebrovascular disease, dementia, diabetes, gastrointestinal disease, heart failure, hypertension, ischemic heart disease, irregular heart rhythm, neurologic disease, nonspecific thyroid disease, osteoporosis, peripheral vascular disease, pituitary disease, psychotic illness, pulmonary disease, renal disease, rheumatic disease, and rheumatic fever. Medications were amiodarone, antidepressants, antiepileptics, β -blockers, kelp, lithium, major tranquilizers, minor tranquilizers, morphine, and steroids.

To allow for a potential clustering effect, primary care practice was included as a random effect. All other confounders were included as fixed effects. Depression score was also included in analyses exploring the association between thyroid status and cognition.

To address the small number of subclinical cases, bootstrapping (22) was used to estimate the accuracy of means and variable estimates in the models. To maintain the structure of the original data, bootstrapping was done by strata (practice), using 1000 replicates, with the number

of participants in each practice fixed to reflect the distribution of the original data set.

Secondary analyses using bootstrapping techniques explored the association between cognition, anxiety, and depression and TSH and free T₄ levels as continuous variables. Association between thyroid category and each of the separate measures of cognitive function as measured by MEAMS were also explored. Sensitivity analyses explored the effect of including TSH and free T₄ values for participants whose thyroid status could not be categorized and those with overt disease.

Role of the Funding Sources

The study was funded by the Healthcare Foundation and received support from the Primary Care Research and Clinical Trials Unit and the Midlands General Practice Research Consortium. Sue Wilson was funded by a Department of Health Career Scientist Award. The funding bodies had no influence on study design, conduct, and reporting. The Healthcare Foundation funded direct research, and the Primary Care Research and Clinical Trials Unit funded service support.

RESULTS

Participants

Practices provided details on 16 125 eligible patients who were contacted. Of these, 339 had died, had moved away, or confirmed ineligibility. A response rate of 85% ($n = 13\ 406$) was achieved, of which 6159 patients (46%) indicated willingness to participate and 5960 attended for screening. At the point of screening, a further 29 patients were deemed ineligible. Forty-four patients were excluded because insufficient blood was obtained for thyroid function testing, and 19 patients did not participate in testing of cognition or mood. Twenty-two patients did not complete the MMSE, and 41 did not complete the MEAMS (Appendix Figure, available at www.annals.org). The main reason for incomplete data was the patients' inability to complete some of the tests owing to poor hearing, language barriers, visual impairment, physical disability, illiteracy, or

curtailment of the assessment because of fatigue. Because the number of patients who did not complete these assessments was small, we cannot identify systematic differences between those who could and could not complete the tests. However, the small numbers involved and practical reasons for inability to complete the tests (for example, inability to see visual tasks) suggest that this had a minimal effect on analyses. Data were therefore obtained for 5868 patients (37% of eligible patients).

Participants ranged in age from 65 to 98 years (mean age, 73.6 years [SD, 5.6]), and 2985 (50.9%) were female. Fifteen participants were categorized as overtly hyperthyroid, 127 as subclinically hyperthyroid, 5524 as euthyroid, 168 as subclinically hypothyroid, and 23 as overtly hypothyroid. Eleven participants could not be categorized and were therefore excluded from analyses (Table 1). Table 2 shows categorical distribution by age and sex.

Association between Thyroid Function and Depression or Anxiety

One hundred thirty-six participants (2.3%) had abnormal depression scores, and 370 participants (6.3%) had abnormal anxiety scores. Unadjusted analyses (model 1) indicated a statistically significant difference among thyroid status categories for anxiety and depression: Participants with overt but undiagnosed hyperthyroidism had lower levels of anxiety than did participants with subclinical hyperthyroidism or those who were euthyroid (maximum difference, 2.01 [95% CI, 0.55 to 3.46]) and lower depression scores compared with all other groups (maximum difference, 1.83 [CI, 0.84 to 2.83]) (Table 3). Subclinically hyperthyroid participants had significantly higher depression scores than did euthyroid participants (maximum difference, 0.84 [CI, 0.21 to 1.47]; $P = 0.009$). Depression scores did not differ between subclinically hypothyroid participants and euthyroid participants (maximum difference, 0.17 [CI, -0.27 to 0.60]; $P = 0.45$). Subclinically hyperthyroid individuals had higher anxiety scores than euthyroid individuals (maximum difference, 0.75 [CI, -0.001 to 1.52]), although this difference was of borderline statistical significance ($P = 0.054$). For anxiety score, no significant difference was found between euthyroid participants and subclinically hyperthyroid or subclinically hypothyroid participants (maximum difference, 0.30 [CI, -0.28 to 0.87]; $P = 0.31$). Only the between-group differences for participants with undiagnosed overt hyperthyroidism remained in adjusted analyses (model 5) (maximum difference in HADS anxiety score, 2.17 [CI, 0.67 to 3.67]; maximum difference in HADS depression score, 1.72 [CI, 0.72 to 2.72]). Differences between subclinically hyperthyroid and euthyroid individuals observed in unadjusted analyses were reduced in the adjusted model (maximum difference in HADS anxiety score, 0.64 [CI, -0.12 to 1.39] [$P = 0.098$]; maximum difference in HADS depression score, 0.61 [CI, 0 to 1.21] [$P = 0.050$]). Table 3

Table 2. Thyroid Status, by Age and Sex

Thyroid Status	Sex, n (%)		Mean Age (SD), y
	Male	Female	
Overt hyperthyroidism	6 (40)	9 (60)	73.1 (6.0)
Subclinical hyperthyroidism	55 (43)	72 (57)	74.6 (5.5)
Euthyroidism			
Quartile 1	778 (53)	693 (47)	73.1 (5.7)
Quartile 2	782 (55)	646 (45)	73.0 (5.6)
Quartile 3	632 (48)	682 (52)	72.8 (5.5)
Quartile 4	559 (43)	752 (57)	73.0 (5.5)
Subclinical hypothyroidism	60 (36)	108 (64)	74.0 (5.8)
Overt hypothyroidism	11 (48)	12 (52)	73.3 (4.9)
Uncategorizable	0 (0)	11 (100)	74.3 (6.3)
Total	2883 (49)	2985 (51)	73.0 (5.6)

Table 3. Thyroid Status and Anxiety and Depression: Mixed-Model Analyses*

Instrument and Model†	Thyroid Status‡							
	Overt Hyperthyroidism	Subclinical Hyperthyroidism	Euthyroidism				Subclinical Hypothyroidism	Overt Hypothyroidism
			Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Mean HADS anxiety score (95% CI)								
Model 1	3.43 (2.18–4.67)	5.44 (4.69–6.18)	4.82 (4.65–4.99)	4.79 (4.61–4.97)	4.69 (4.51–4.86)	4.89 (4.71–5.08)	4.98 (4.43–5.53)	4.20 (3.17–5.22)
Model 2	3.18 (2.01–4.35)	5.44 (4.72–6.16)	4.92 (4.75–5.09)	4.94 (4.76–5.12)	4.71 (4.53–4.89)	4.82 (4.63–5.01)	4.85 (4.32–5.38)	4.20 (3.24–5.16)
Model 3	3.12 (1.94–4.29)	5.38 (4.65–6.10)	4.88 (4.71–5.05)	4.90 (4.72–5.08)	4.68 (4.50–4.86)	4.78 (4.59–4.97)	4.83 (4.30–5.36)	4.11 (3.17–5.06)
Model 4	3.16 (1.89–4.43)	5.33 (4.60–6.05)	4.87 (4.70–5.04)	4.90 (4.72–5.09)	4.69 (4.51–4.87)	4.78 (4.59–4.97)	4.85 (4.33–5.38)	4.09 (3.19–4.99)
Model 5	3.15 (1.86–4.45)	5.33 (4.59–6.06)	4.85 (4.68–5.01)	4.89 (4.71–5.07)	4.69 (4.51–4.86)	4.76 (4.57–4.94)	4.79 (4.31–5.28)	4.05 (3.07–5.04)
Mean HADS depression score (95% CI)								
Model 1	2.32 (1.54–3.11)	4.16 (3.55–4.76)	3.48 (3.34–3.62)	3.54 (3.39–3.68)	3.32 (3.18–3.46)	3.45 (3.30–3.59)	3.48 (3.07–3.90)	3.68 (2.64–4.71)
Model 2	2.31 (1.46–3.15)	4.12 (3.52–4.73)	3.60 (3.46–3.74)	3.68 (3.53–3.83)	3.44 (3.29–3.58)	3.51 (3.37–3.66)	3.53 (3.11–3.95)	3.79 (2.81–4.77)
Model 3	2.22 (1.37–3.06)	4.03 (3.43–4.64)	3.53 (3.39–3.67)	3.62 (3.47–3.77)	3.39 (3.24–3.54)	3.46 (3.31–3.60)	3.49 (3.08–3.91)	3.66 (2.69–4.62)
Model 4	2.39 (1.55–3.23)	3.99 (3.40–4.58)	3.51 (3.37–3.64)	3.61 (3.47–3.75)	3.38 (3.24–3.52)	3.44 (3.30–3.58)	3.50 (3.09–3.91)	3.69 (2.74–4.64)
Model 5	2.27 (1.44–3.09)	3.99 (3.41–4.58)	3.49 (3.36–3.62)	3.61 (3.47–3.75)	3.39 (3.25–3.53)	3.43 (3.28–3.57)	3.42 (3.04–3.80)	3.66 (2.70–4.62)

* HADS = Hospital Anxiety and Depression Scale.

† Model 1 includes thyroid status only; model 2 includes model 1 plus age, sex, and practice (random effect); model 3 includes model 2 plus deprivation; model 4 includes model 3 plus comorbid conditions; and model 5 includes model 4 plus specified medications. Comorbid conditions and medications are listed in the text.

‡ Sample for analysis consisted of 5857 patients. Eleven patients were excluded because their thyroid status could not be categorized.

shows mean anxiety and depression scores by thyroid status for all analyses.

Unadjusted analyses (model 1) indicated no association between TSH or free T₄ level and anxiety ($P = 0.137$ and 0.58 , respectively) (Table 4). No evidence of an association between TSH level and depression was observed ($P = 0.93$), but a significant association between free T₄ level and depression was found ($P = 0.004$). Adjusted analyses confirmed the lack of association between anxiety and free T₄ level ($P = 0.51$) but demonstrated a significant association with TSH level ($P = 0.013$), such that a 50-

mIU/L increase in TSH level is associated with a 1-point reduction in HADS anxiety score. Adjusted analyses showed no association between depression and TSH level ($P = 0.74$) or free T₄ level ($P = 0.092$). The result for free T₄ level did not reach a conventional degree of statistical significance, but this may be due in part to the small number of participants with subclinical disease. The effect size, whereby a 36-pmol/L change in free T₄ level would be required for a 1-unit change in depression score, shows that this finding is not clinically relevant.

Sensitivity analyses that included participants whose

Table 4. Association between Thyroid-Stimulation Hormone and Free Thyroxine Levels and Anxiety, Depression, and Cognition*

Instrument and Hormonet	Coefficient ± SE‡					P Value§
	Model 1	Model 2	Model 3	Model 4	Model 5	
HADS anxiety score						
TSH level	-0.013 ± 0.0085	-0.022 ± 0.0083	-0.022 ± 0.0082	-0.023 ± 0.0082	-0.023 ± 0.0091	0.013
Free T ₄ level	0.012 ± 0.021	0.022 ± 0.021	0.023 ± 0.021	0.006 ± 0.021	0.014 ± 0.021	0.51
HADS depression score						
TSH level	-0.0007 ± 0.0076	-0.0025 ± 0.007	-0.0021 ± 0.0075	-0.0029 ± 0.0078	-0.0025 ± 0.0076	0.74
Free T ₄ level	0.050 ± 0.017	0.041 ± 0.017	0.043 ± 0.017	0.026 ± 0.017	0.028 ± 0.016	0.092
MEAMS score						
TSH level	0.0036 ± 0.0025	0.0049 ± 0.0027	0.0049 ± 0.0029	0.0049 ± 0.0029	0.0046 ± 0.0028	0.106
Free T ₄ level	0.0010 ± 0.0065	0.0094 ± 0.0063	0.0084 ± 0.0062	0.010 ± 0.0063	0.0088 ± 0.0063	0.162
MMSE score						
TSH level	0.018 ± 0.0049	0.019 ± 0.0050	0.019 ± 0.0051	0.019 ± 0.0051	0.020 ± 0.0051	<0.001
Free T ₄ level	0.035 ± 0.013	0.038 ± 0.013	0.037 ± 0.012	0.043 ± 0.013	0.042 ± 0.013	<0.001

* HADS = Hospital Anxiety and Depression Scale; MEAMS = Middlesex Elderly Assessment of Mental State; MMSE = Mini-Mental State Examination; T₄ = thyroxine; TSH = thyroid-stimulating hormone.

† Samples for analysis consisted of 5857 patients for HADS, 5816 patients for MEAMS, and 5835 patients for the MMSE. Patients whose thyroid status could not be categorized were excluded.

‡ Coefficients indicate the change in outcome score associated with a 1-mIU/L increase in TSH level or 1-pmol/L increase in free T₄ level. Model 1 includes thyroid status only; model 2 includes model 1 plus age, sex, and practice (random effect); model 3 includes model 2 plus deprivation; model 4 includes model 3 plus comorbid conditions; and model 5 includes model 4 plus specified medications. Comorbid conditions and medications are listed in the text.

§ P values are derived from the fully adjusted analysis (model 5).

Table 5. Association between Thyroid Status and Cognition: Mixed-Model Analyses*

Instrument and Model†	Thyroid Status					
	Overt Hyperthyroidism	Subclinical Hyperthyroidism	Euthyroidism			
			Quartile 1	Quartile 2	Quartile 3	Quartile 4
Mean MEAMS score (95% CI)						
Model 1	11.25 (10.65–11.85)	11.24 (11.05–11.44)	11.40 (11.35–11.46)	11.39 (11.33–11.44)	11.43 (11.37–11.48)	11.39 (11.33–11.46)
Model 2	11.30 (10.69–11.91)	11.29 (11.10–11.47)	11.35 (11.29–11.40)	11.32 (11.26–11.38)	11.36 (11.30–11.41)	11.35 (11.29–11.42)
Model 3	11.35 (10.75–11.96)	11.34 (11.16–11.53)	11.39 (11.34–11.45)	11.36 (11.31–11.42)	11.39 (11.34–11.44)	11.39 (11.33–11.46)
Model 4‡	11.44 (10.92–11.95)	11.33 (11.15–11.52)	11.39 (11.34–11.45)	11.36 (11.31–11.42)	11.39 (11.34–11.44)	11.39 (11.33–11.46)
Model 5‡	11.42 (10.91–11.93)	11.34 (11.15–11.52)	11.39 (11.34–11.44)	11.37 (11.31–11.43)	11.39 (11.33–11.44)	11.39 (11.33–11.45)
Mean MMSE score (95% CI)						
Model 1	28.44 (27.62–29.27)	27.85 (27.47–28.23)	27.94 (27.83–28.05)	27.96 (27.84–28.07)	28.00 (27.89–28.12)	27.92 (27.80–28.05)
Model 2	28.49 (27.82–29.15)	27.93 (27.58–28.28)	27.86 (27.75–27.97)	27.87 (27.75–27.98)	27.89 (27.78–28.00)	27.87 (27.74–27.99)
Model 3	28.59 (27.89–29.29)	28.04 (27.68–28.40)	27.94 (27.83–28.05)	27.94 (27.83–28.06)	27.95 (27.83–28.06)	27.94 (27.82–28.06)
Model 4‡	28.51 (27.73–29.30)	28.07 (27.72–28.43)	27.95 (27.84–28.06)	27.95 (27.84–28.07)	27.94 (27.83–28.06)	27.94 (27.82–28.07)
Model 5‡	28.53 (27.72–29.34)	28.06 (27.71–28.42)	27.95 (27.84–28.06)	27.96 (27.85–28.07)	27.94 (27.83–28.05)	27.95 (27.83–28.07)

* MEAMS = Middlesex Elderly Assessment of Mental State; MMSE = Mini-Mental State Examination.
 † Samples for analysis consisted of 5857 patients for Hospital Anxiety and Depression Scale (HADS), 5816 patients for MEAMS, and 5835 patients for the MMSE. Patients whose thyroid status could not be categorized were excluded. Model 1 includes thyroid status only; model 2 includes model 1 plus age, sex, and practice (random effect); model 3 includes model 2 plus deprivation; model 4 includes model 3 plus comorbid conditions; and model 5 includes model 4 plus specified medications. Comorbid conditions and medications are listed in the text.
 ‡ Also includes HADS depression score.

thyroid function test results were uncategorizable did not alter these findings. Exclusion of participants with overt disease from analyses of TSH and free T₄ produced similar results in terms of coefficients, but TSH level was no longer significantly related to anxiety ($P = 0.12$). Confounding variables, including deprivation score, age, sex, presence of many comorbid conditions (such as hypertension and diabetes), and medication use (such as antidepressants and steroids), were significantly associated with both depression and anxiety. Increased levels of anxiety and depression were associated with being female ($P < 0.001$) and having a greater deprivation score ($P < 0.001$). Increasing age was associated with an increase in depression score but a decrease in anxiety score ($P < 0.001$).

Association between Thyroid Function and Cognitive Functioning

Of the 5864 participants who completed the MMSE, 305 (5.2%) had scores indicative of cognitive dysfunction. Unadjusted analyses (Table 5, model 1) demonstrated no differences in cognitive functioning between thyroid groups when the MEAMS or MMSE was considered the indicator of cognitive function. Adjusted analyses (Table 5, model 5) did not alter this finding.

Analyses that included TSH and free T₄ levels as continuous variables (Table 4) demonstrated no association between cognition and free T₄ level according to results on the MEAMS ($P = 0.87$) or MMSE ($P = 0.28$). An association between MMSE score and TSH level was seen ($P < 0.001$), but information from MEAMS did not support this finding ($P = 0.147$). Adjusted analyses indicated no association between MEAMS score and TSH ($P =$

0.106) or free T₄ level ($P = 0.162$), and no association was found with any of the subscales that measured discrete aspects of cognitive function. However, when the MMSE was considered the measure of cognitive function, associations with both TSH and free T₄ levels were found ($P < 0.001$): A 1-point increase in MMSE score was associated with a 50-mIU/L increase in TSH level and a 25-pmol/L increase in free T₄ level.

Sensitivity analyses that included participants whose thyroid function tests were uncategorizable did not alter these findings. The exclusion of participants with overt but unrecognized disease again produced similar results in terms of coefficients, but TSH level was no longer related to cognition as measured by the MMSE score ($P = 0.29$). Confounding variables that were associated with cognitive function scores in the final adjusted model were deprivation, age, sex, depression score, presence of many comorbid conditions, and use of medications. Reduced cognitive functioning was associated with being female ($P < 0.006$), increasing age ($P < 0.001$), and higher levels of deprivation ($P < 0.001$).

DISCUSSION

Thyroid dysfunction, cognitive dysfunction, and depression are all common problems among elderly persons, and the possibility that thyroid dysfunction might be a causal factor in cognitive dysfunction and depression is important, particularly because treatment of thyroid dysfunction is relatively straightforward. Previous reports of associations between these conditions have been conflict-

Table 5—Continued

Subclinical Hypothyroidism	Overt Hypothyroidism
11.44 (11.30–11.57)	11.70 (11.51–11.88)
11.39 (11.25–11.53)	11.64 (11.42–11.86)
11.42 (11.28–11.56)	11.73 (11.49–11.97)
11.42 (11.28–11.56)	11.72 (11.48–11.96)
11.43 (11.30–11.57)	11.70 (11.45–11.95)
28.11 (27.81–28.42)	28.51 (27.64–29.38)
28.02 (27.72–28.32)	28.37 (27.52–29.23)
28.07 (27.76–28.37)	28.54 (27.69–29.39)
28.07 (27.78–28.37)	28.53 (27.70–29.37)
28.08 (27.79–28.38)	28.57 (27.72–29.43)

ing, and a systematic review of the literature was inconclusive (1). The conflicting findings of previous studies may be attributable to various factors, such as small sample size, selection or inclusion criteria, and differing definitions of subclinical dysfunction, but may also be due in part to lack of control for potential confounding variables, such as comorbid conditions and medication use. Our findings derive from a large community-based sample (5868 patients ≥ 65 years of age who were recruited from 20 primary care practices) and are based on standard laboratory reference ranges. Evidence is robust that for patients without clinically determined disease, no clinically relevant association exists between thyroid function and cognitive function, anxiety, or depression.

The lack of association between subclinical hypothyroidism and cognitive function in our study confirms findings reported elsewhere (5, 7, 8). We identified a small but statistically significant positive correlation between both TSH and free T_4 values and cognitive functioning as measured by the MMSE, but this correlation was not found when MEAMS, which is a more detailed and sensitive measure of cognitive function, was used. Moreover, the association has no clinical relevance because an increase of 50 mIU/L in TSH level or 25 pmol/L in free T_4 level would be required to demonstrate a 1-unit increase in MMSE score. This finding is therefore a statistical artifact of the large sample size and, given the lack of association with MEAMS score, may be a chance occurrence. Sensitivity analyses in which patients with overt but unrecognized disease were excluded demonstrated no statistically significant association with TSH level, suggesting that the

association was highly sensitive to the inclusion of these few atypical patients with high TSH levels. This finding further highlights the lack of association between cognition and subclinical dysfunction.

Our study also confirms the findings of other recent studies of thyroid function (11, 15) in that no association was seen between subclinical dysfunction and depression. An association between TSH level and anxiety was also sensitive to inclusion of a few participants with overt unrecognized disease and did not persist when these participants were excluded. Again, any statistically significant association has no clinical implications, because a 1-unit reduction in HADS anxiety score would require a 50-mIU/L increase in TSH level. We did not observe a lower prevalence of depression in persons with overt hypothyroidism, as Engum and colleagues reported (15); however, the number of patients with overt hypothyroidism in our study was low because the study was designed to determine associations with subclinical dysfunction. Persons known to have current or recently treated overt disease were therefore excluded. The small number of participants with previously unidentified overt disease was insufficient to robustly explore this association further.

Of note, we adjusted for comorbid conditions and medication use. After adjustment for these factors, associations between thyroid function and cognition and depression disappeared. The decrease in coefficients for free T_4 level between models 3 and 4 in the HADS analysis, for example, suggests an important confounding role of chronic disease. The finding of statistically significant associations between depression and coexisting chronic disease states, such as diabetes (23, 24) or chronic lung disease (25, 26), or concurrent use of medications, such as antidepressants (25) or steroids (26, 27), is to be expected. Statistically significant associations are also seen, as expected, between cognitive functioning and coexisting chronic diseases (such as dementia) and medication use (such as antidepressants) (28). Earlier, smaller studies that reported associations with subclinical disease and depression (6, 10, 12, 13) and cognitive decline (10) did not include adjustment for comorbid conditions or medication use; these confounders may therefore explain the positive associations that we did not confirm in the Birmingham Elderly Thyroid Study.

The prevalence of subclinical dysfunction was lower than expected at the outset of the study (2.9% of patients with subclinical hypothyroidism and 2.2% of patients with subclinical hyperthyroidism). Exclusion of patients currently receiving therapy for thyroid dysfunction resulted in exclusion of some patients with subclinical dysfunction who were being treated by their clinicians. Screening for and treatment of subclinical disease may occur more frequently within primary care settings in Birmingham because the area has been a focus of previous thyroid research. Overall, the community-based approach and large screened population are likely to have generated a more

representative sample than was obtained in previous studies. The lack of association between cognition, depression, or anxiety and TSH and free T₄ levels supports the primary categorical findings, and the lower-than-expected prevalence of subclinical dysfunction is therefore unlikely to have substantially affected our results.

The uptake rate in our study (38% of persons contacted) may be a limitation, although responders were representative of the regional population (29) with respect to age, sex, and level of deprivation. However, a systematic bias may have occurred if persons who presented for screening were the least frail persons. The availability of home visits aimed to minimize such selection bias. Furthermore, comparison of morbidity data from our screened sample with prevalence estimates for the United Kingdom population (30) does not indicate that participants were healthier than the general population. For example, the prevalence of diabetes was slightly higher in the study sample than morbidity data from United Kingdom general practices suggest for the overall population (7.3% compared with 6.4% of women 65 to 75 years of age and 11.5% compared with 8.5% of men 65 to 75 years of age), whereas coronary heart disease was less common in the study sample (5.6% compared with 17.2% of women 65 to 75 years of age and 11.2% compared with 18.4% of men 65 to 75 years of age).

Our data, which are based on a large sample drawn from the general population, confirm the lack of association between subclinical thyroid dysfunction and cognitive impairment and mood. These findings should help dispel the uncertainty generated by numerous studies of limited quality or size and provide guidance for physicians who must interpret increasing numbers of subclinical thyroid function test results. Previous studies demonstrating an association may have done so because other explanatory variables were insufficiently controlled for. Our data do not support the need to screen patients for subclinical thyroid dysfunction with a view to arresting or reversing cognitive decline or depressive illness, and they provide no rationale for therapeutic intervention in such patients on the basis of modifying cognitive or mood outcomes. Furthermore, our findings do not support decreasing the upper limit of the normal reference range of serum TSH level. We encourage full evaluation of other relevant outcomes in large community-based samples.

From the University of Birmingham, Birmingham, United Kingdom.

Acknowledgments: The authors thank the practices and patients who participated in this study; the practice nurses and health care assistants who undertook the screening tests and saw patients on their behalf; and the staff of the Regional Endocrine Laboratory, University Hospital Birmingham National Health Service Foundation Trust. They also thank the other members of the Research Team and Steering Group: Mrs. Rhona Alekna (Research Nurse), Mrs. Pam Bridge (Project Officer), Mrs. Jacqui Cannon (Research Nurse), Dr. Michael Gammage (Cardiologist), Mr. Roger Holder (Statistician), Mrs. Elaine Kidney (Research

Associate), Ms. Rose Nolan (Research Nurse), Mrs. Jo-Anne Miles (Research Nurse), Mrs. Val Redman (Senior Project Officer), Professor Michael Sheppard (Endocrinologist), Ms. Dawn Swancutt (Research Associate), and Mrs. Sally Warmington (Project Officer).

Grant Support: The study was funded by the Healthcare Foundation and received support from the Primary Care Research and Clinical Trials Unit and the Midlands GP Research Consortium. Sue Wilson was funded by a Department of Health Career Scientist Award. The Healthcare Foundation funded direct research, and the Primary Care Research and Clinical Trials Unit funded service support.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Lesley M. Roberts, PhD, Department of Primary Care and General Practice, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom; e-mail, l.m.roberts@bham.ac.uk.

Current author addresses and author contributions are available at www.annals.org.

References

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004;291:228-38. [PMID: 14722150]
2. Ringel MD, Mazzaferri EL. Subclinical thyroid dysfunction—can there be a consensus about the consensus? [Editorial] *J Clin Endocrinol Metab*. 2005;90:588-90. [PMID: 15643021]
3. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT, et al. Consensus Statement #1: subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. *Thyroid*. 2005;15:24-8. [PMID: 15687817]
4. Stern RA, Prange AJ Jr. Neuropsychiatric aspects of endocrine disorders. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*. Baltimore: Williams & Wilkins; 1995:241-51.
5. Osterweil D, Syndulko K, Cohen SN, Pettler-Jennings PD, Hershman JM, Cummings JL, et al. Cognitive function in non-demented older adults with hypothyroidism. *J Am Geriatr Soc*. 1992;40:325-35. [PMID: 1556359]
6. van Bostel MP, Menheere PP, Bekers O, Hogervorst E, Jolles J. Thyroid function, depressed mood, and cognitive performance in older individuals: the Maastricht Aging Study. *Psychoneuroendocrinology*. 2004;29:891-8. [PMID: 15177704]
7. Luboshitzky R, Oberman AS, Kaufman N, Reichman N, Flatau E. Prevalence of cognitive dysfunction and hypothyroidism in an elderly community population. *Isr J Med Sci*. 1996;32:60-5. [PMID: 8550351]
8. Bono G, Fancellu R, Blandini F, Santoro G, Mauri M. Cognitive and affective status in mild hypothyroidism and interactions with L-thyroxine treatment. *Acta Neurol Scand*. 2004;110:59-66. [PMID: 15180808]
9. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;292:2591-9. [PMID: 15572717]
10. Monzani F, Del Guerra P, Caraccio N, Pruneti CA, Pucci E, Luisi M, et al. Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clin Investig*. 1993;71:367-71. [PMID: 8508006]
11. Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *J Clin Endocrinol Metab*. 2006;91:145-53. [PMID: 16263815]
12. Haggerty JJ Jr, Stern RA, Mason GA, Beckwith J, Morey CE, Prange AJ Jr. Subclinical hypothyroidism: a modifiable risk factor for depression? *Am J Psychiatry*. 1993;150:508-10. [PMID: 8434671]
13. Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, Crook M, et al. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med*. 2002;112:348-54. [PMID: 12111111]

11904108]

14. **Sait Gonen M, Kisakol G, Savas Cilli A, Dikbas O, Gungor K, Inal A, et al.** Assessment of anxiety in subclinical thyroid disorders. *Endocr J.* 2004;51:311-5. [PMID: 15256776]
15. **Engum A, Bjoro T, Mykletun A, Dahl AA.** An association between depression, anxiety and thyroid function—a clinical fact or an artefact? *Acta Psychiatr Scand.* 2002;106:27-34. [PMID: 12100345]
16. **Noble M, Wright G, Dibben C, et al.** The English Indices of Deprivation 2004 (Revised). London: Neighbourhood Renewal Unit, Report to the Office of the Deputy Prime Minister; 2004.
17. **Folstein MF, Folstein SE, McHugh PR.** “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-98. [PMID: 1202204]
18. **Golding E.** The Middlesex Elderly Assessment of Mental State. Bury St. Edmonds, Suffolk: Thames Valley Test Company; 1989.
19. **Zigmond AS, Snaith RP.** The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67:361-70. [PMID: 6880820]
20. **Bravo G, Hébert R.** Age- and education-specific reference values for the Mini-Mental and modified Mini-Mental State Examinations derived from a non-demented elderly population. *Int J Geriatr Psychiatry.* 1997;12:1008-18. [PMID: 9395933]
21. **Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM.** A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med.* 1997;27:363-70. [PMID: 9089829]
22. **Efron B, Tibshirani R.** *An Introduction to the Bootstrap.* New York: Chapman and Hall; 1993.
23. **Talbot F, Nouwen A.** A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care.* 2000;23:1556-62. [PMID: 11023152]
24. **Egede LE.** Diabetes, major depression, and functional disability among U.S. adults. *Diabetes Care.* 2004;27:421-8. [PMID: 14747223]
25. **Patten SB, Beck CA, Kassam A, Williams JV, Barbui C, Metz LM.** Long-term medical conditions and major depression: strength of association for specific conditions in the general population. *Can J Psychiatry.* 2005;50:195-202. [PMID: 15898458]
26. **Gift AG, Wood RM, Cahill CA.** Depression, somatization and steroid use in chronic obstructive pulmonary disease. *Int J Nurs Stud.* 1989;26:281-6. [PMID: 2767912]
27. **Brown ES, Suppes T.** Mood symptoms during corticosteroid therapy: a review. *Harv Rev Psychiatry.* 1998;5:239-46. [PMID: 9493946]
28. **Barnes DE, Alexopoulos GS, Lopez OL, Williamson JD, Yaffe K.** Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. *Arch Gen Psychiatry.* 2006;63:273-9. [PMID: 16520432]
29. **Office for National Statistics.** 2001 Census National Report for England and Wales. Palgrave: Macmillan; 2004.
30. **Office for National Statistics.** Key Health Statistics from General Practice 1998. London: National Statistics; 2000.

Current Author Addresses: Dr. Roberts, Professors Wilson, Hobbs, and Parle, and Mrs. Roalfe: Department of Primary Care and General Practice, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom.

Dr. Pattison: School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham B4 7ET, United Kingdom.

Professor Franklyn: Department of Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom.

Author Contributions: Conception and design: L.M. Roberts, H. Pattison, A. Roalfe, J. Franklyn, S. Wilson, F.D.R. Hobbs, J.V. Parle.

Analysis and interpretation of the data: L.M. Roberts, H. Pattison, A. Roalfe, J. Franklyn, S. Wilson, F.D.R. Hobbs, J.V. Parle.

Drafting of the article: L.M. Roberts, A. Roalfe.

Critical revision of the article for important intellectual content: L.M. Roberts, H. Pattison, A. Roalfe, J. Franklyn, S. Wilson, F.D.R. Hobbs, J.V. Parle.

Final approval of the article: L.M. Roberts, H. Pattison, A. Roalfe, J. Franklyn, S. Wilson, F.D.R. Hobbs, J.V. Parle.

Provision of study materials or patients: L.M. Roberts.

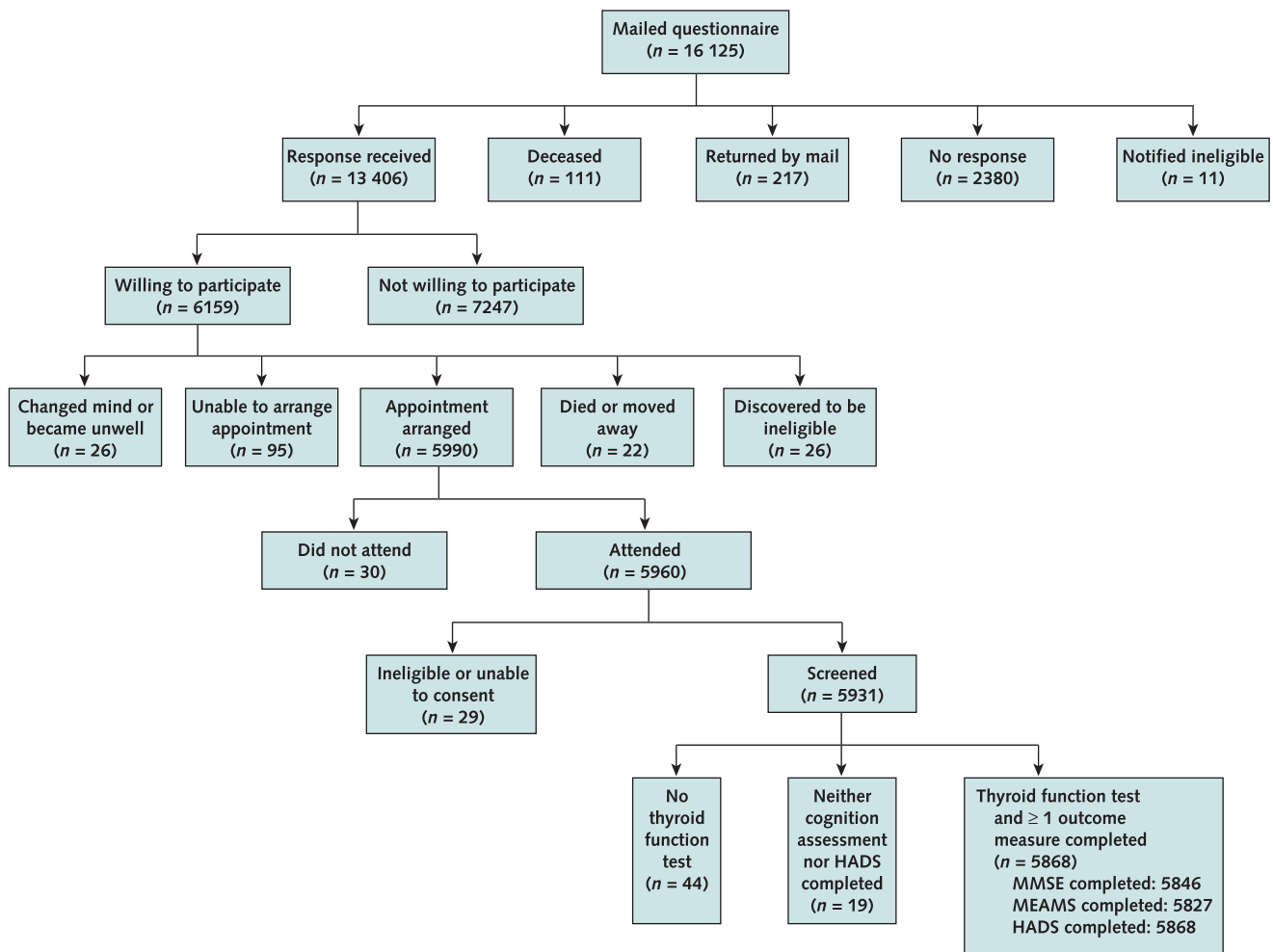
Statistical expertise: A. Roalfe.

Obtaining of funding: H. Pattison, A. Roalfe, J. Franklyn, S. Wilson, F.D.R. Hobbs, J.V. Parle.

Administrative, technical, or logistic support: L.M. Roberts, S. Wilson.

Collection and assembly of data: L.M. Roberts.

Appendix Figure. Recruitment flow chart.



HADS = Hospital Anxiety and Depression Scale; MEAMS = Middlesex Elderly Assessment of Mental State; MMSE = Mini-Mental State Examination.