Published in final edited form as:
J Am Geriatr Soc. 2009 January ; 57(1): 89–93. doi:10.1111/j.1532-5415.2008.02080.x.

Thyroid Function Abnormalities and Cognitive Impairment in the Elderly. Results of the InCHIANTI Study

Graziano Ceresini, MD[1], **Fulvio Lauretani, MD**[2], **Marcello Maggio, MD**[1], **Gian Paolo Ceda, MD**[1], **Simonetta Morganti, MD**[1], **Elisa Usberti, MD**[1], **Carlo Chezzi, MD**[3], **Rita Valcavi, MD**[1], **Stefania Bandinelli, MD**[4], **Jack M. Guralnik, MD**[5], **Anne R. Cappola, MD, ScM**[6], **Giorgio Valenti, MD**[1], and **Luigi Ferrucci, MD, PhD**[7]

[1]Department of Geriatrics- Endocrine Unit, University of Parma, Parma, Italy

[2]ARS Toscana, Firenze, Italy

[3]Department of Pathology and Laboratory Medicine, University of Parma, Italy

[4]Geriatric Unit, ASF Toscana, Firenze, Italy

[5]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Baltimore, MD, USA

[6]University of Pennsylvania School of Medicine, Philadelphia, PA, USA

[7]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, MD, USA

Abstract

Objectives—To investigate thyroid function testing abnormalities in older persons and to explore the relationship between thyroid dysfunction and cognition.

Design—Cross-sectional study

Setting—Community-based

Participants—1171 men and women aged 23-102 yrs

Measurements—Thyroid function was evaluated by measuring plasma concentrations of thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3). Cognition was evaluated by the Mini Mental State Examination (MMSE).

Prevalence of overt and subclinical thyroid dysfunction was evaluated in different age groups (<65 versus ≥65 years). Age trends in TSH, FT4, and FT3 were examined in euthyroid participants. The cross-sectional association of thyroid dysfunction with MMSE score was evaluated adjusting for confounders.

Results—Both subclinical hypothyroidism and subclinical hyperthyroidism were more prevalent in older than in younger participants (Subclinical hypothyroidism, 0.4 % vs 3.5 % in younger vs older participants, respectively, *P*<.03 Subclinical hyperthyroidism, 1.9 % vs 7.8 % in younger vs

Corresponding Author : Graziano Ceresini, M.D., Department of Internal Medicine and Biomedical Sciences, Section of Geriatrics-Endocrine Unit, Via Gramsci, 14-43100 Parma, Italy, Ph: 011-39-0521-986843, Fax: 011-39-0521-987562, e-mail: ceresini@unipr.it.
Author contributions: All the listed authors contributed toward the concept, design, data analysis, preparation of the paper, etc. on this paper.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Sponsor's Role: none

older participants, respectively, *P*<.002). In euthyroid participants TSH and FT3 declined with age while FT4 increased. Old participants with subclinical hyperthyroidism had a lower MMSE score than euthyroid subjects (22.61 ± 6.88 vs 24.72 ± 4.52, *P*<.03). In adjusted analyses, participants with subclinical hyperthyroidism were significantly more likely to have cognitive dysfunction (HR: 2.26, *P*= .003).

Conclusion—Subtle age-related changes in FT3, FT4 and TSH occur in individuals who remain euthyroid. Subclinical hyperthyroidism is the most prevalent thyroid dysfunction in Italian older persons and is associated with cognitive impairment.

Keywords

Thyroid function; Aging; Cognition

INTRODUCTION

Changes in thyroid function participate in the overall readjustment of the hormonal milieu that occurs with aging (1). The prevalence of overt and subclinical hypothyroidism in older populations is as high as 20% (3). Subclinical hyperthyroidism also increases with aging, with a prevalence of 1-2 % in iodine-sufficient areas (3,4) and 7-8 % in iodine-deficient areas (5). Whether subclinical thyroid dysfunction affects health and functional status in older persons is still unclear (6,7). Epidemiological studies that have investigated the relationship between subclinical hypothyroidism (8,9) or subclinical hyperthyroidism (3,10) and impaired cognition have reported inconsistent findings. The lack of consistency between studies may depend on different assay methods, different diagnostic criteria for thyroid dysfunction, and different assessments of cognition. Moreover, many of these studies were clinical case series that may not be representative of the general population.

We measured thyrotropin (TSH) and thyroid hormone concentrations in the participants of the InCHIANTI study, an epidemiological study conducted on a population-based sample of persons living in the Chianti geographical area (Tuscany, Italy). Using these data, we explored age-related trends in thyroid hormone levels and we estimated the prevalence of subclinical and overt hypothyroidism and hyperthyroidism in the older population. In addition, we evaluated whether subclinical thyroid dysfunction is cross-sectionally associated with cognitive impairment independent of potential confounders, such as, chronic heart failure, smoking, and physical activity.

METHODS

The study population consisted of men and women, aged 23-102 years, who participated in the Invecchiare in Chianti, “Aging in the Chianti Area” (InCHIANTI) study, conducted in two small towns in Tuscany, Italy. The rationale, design, and data collection have been described elsewhere (11). Of the 1453 participants who had home interviews, 1343 (92%) donated a blood sample. Complete data on both thyroid hormones and cognitive performance were available in 1208 participants. Participants who were on chronic treatment with drugs known to affect thyroid function, such as thyroid hormone preparations, methimazole, propylthiouracil, amiodarone, and lithium, were excluded from the analyses. Three participants affected by dementia were also excluded. The final study population included 1171 subjects (652 women and 519 men).

Participants received an extensive description of the study and participated after written, informed consent was obtained. The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee.

Laboratory Measures

Blood samples were collected in the morning after a 12-h fast. Aliquots of serum and plasma were obtained within three hours and stored at -80° C. Plasma concentrations of TSH, free triiodothyronine (FT3), and free thyroxine (FT4) were measured using a chemiluminescent immunoassay (Vitros Reagent, Ortho-Clinical Diagnostics, Johnson & Johnson Medical Section, Milan, Italy). The reference normal ranges were 0.46 to 4.68 mIU/L for TSH, 2.77 to 5.27 pg/mL for FT3, and 0.77 to 2.19 ng/dl for FT4. Assay sensitivities were 0.003 mIU/L for TSH, 0.39 pg/mL for FT3, and 0.03 ng/dL for FT4. Intra-assay coefficient of variations (CVs) were 3.9% to 5.3% over the range 0.06 - 80.11 mIU/L for TSH, 4.4% to 5.1% over the range 2.86 - 11.90 pg/mL for FT3, and 4.5% to 5.3% over the range 0.61 - 3.90 ng/dL for FT4. Interassay CVs were less than 9% for all three hormones.

Cognitive Assessment

Global cognitive performance was assessed by the Mini-Mental State Examination (MMSE) performed by a trained geriatrician within a week of the blood draw. A MMSE value <24 was considered to indicate cognitive impairment (12).

Other Covariates

Information on demographics, smoking and use of medication were collected by a standardized questionnaire. Average daily intake of energy (kcal) and type of nutrition were estimated using the European Prospective Investigation into Cancer and Nutrition food frequency questionnaire, validated in the InCHIANTI population (13). Diseases were ascertained according to standard, pre-established criteria and algorithms that combine information from self-reported physician diagnoses, current pharmacological treatment, medical records, clinical examinations and blood tests (14). Diseases included in the current analysis were congestive heart failure, stroke, diabetes, hypertension, and Parkinson's disease. Weight was measured using a high-precision mechanical scale. Standing height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Based on self-report information, the level of physical activity in the year prior to the interview was coded as 1) hardly any physical activity; 2) mostly sitting (occasionally walks, easy gardening); 3) light exercise (no sweat) 2-4 h/week; 4) moderate exercise (sweat) 1-2 h/week (level 4); 5) moderate exercise >3 h/week; 6) intense exercise (at the limits) > 3 times/week. For analytical purposes, we grouped participants into three levels: (1-3) inactive or light physical activity; (4-5) moderate physical activity; and (6) intense activity. Smoking was coded in the analysis as "current smoking" versus "ever smoked" or "never smoked". Education was recorded as years in school.

Definition of Thyroid Function

Participants were classified, according to TSH and free thyroid hormone concentrations into 5 categories: overt hypothyroidism (TSH >4.68 mIU/L and FT4<0.78 ng/dL), subclinical hypothyroidism (TSH >4.68 mIU/L and FT4 0.77-2.19 ng/dL), euthyroidism (TSH 0.46-4.68 mIU/L), subclinical hyperthyroidism (TSH <0.46 mIU/L, FT4 0.77-2.19 ng/dL and FT3 2.77-5.27 pg/mL), and overt hyperthyroidism (TSH <0.46 mIU/L, with FT4 >2.19 ng/dL and/or FT3 >5.27 pg/mL). Four subjects affected by low-T3 syndrome (FT3<2.77 pg/mL with normal FT4 and TSH) were excluded from analyses.

Statistical Analysis

Variables with normal distribution are reported as mean values ± standard deviations and categorical values as percentages. Analyses were performed after categorizing thyroid function into euthyroidism, hypothyroidism, subclinical hypothyroidism, hyperthyroidism and subclinical hyperthyroidism. Prevalences of the different thyroid function groups

between young (<65 yrs) and old (≥65 yrs) participants were compared using the Chi square test. Differences of population characteristics across thyroid status groups were tested using age-and sex- adjusted linear or multinomial logistic regression models, as appropriate.

Factors significantly correlated with MMSE were identified using age-adjusted partial correlation coefficients and Spearman partial rank-order correlation coefficients, as appropriate. The relationship between subclinical hyperthyroidism and MMSE score was explored by linear regression models that were initially adjusted for age, sex, education, level of physical activity, smoking, stroke, Parkinson's disease, hypertension, chronic heart failure and diabetes. Parsimonious models were subsequently obtained by backward selection. All analyses were performed using the SAS statistical package, version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Characteristics of the study population and prevalence of thyroid dysfunction

Of the 255 participants younger than 65 years (139 women and 116 men), 243 (95%) were euthyroid, one had overt hypothyroidism, one had subclinical hypothyroidism, and 5 (2%) and 5 (2%) had, respectively, overt and subclinical hyperthyroidism (Table 1). Of the 916 participants aged 65 years and older (513 women and 403 men), 800 (87%) were euthyroid, whereas 5 (0.6%) and 25 (2.7%) had, respectively, overt and subclinical hypothyroidism and 15 (1.6%) and 71 (7.8%) had, respectively, overt and subclinical hyperthyroidism (Table 2). Thus, both subclinical hypothyroidism and subclinical hyperthyroidism were more prevalent in older than in younger individuals ($P<.03$ and $P<.002$, respectively), while the prevalence of either overt hypothyroidism ($P= .77$) or overt hyperthyroidism ($P=.93$) were similar in younger and older individuals.

Effect of age on thyrotropin and free thyroid hormone levels in euthyroid participants

In analyses limited to the 1043 participants with normal thyroid function, we found that TSH and FT3 levels were progressively lower ($P=.03$, $P<.001$, respectively) while FT4 levels were progressively higher ($P<.001$) from younger to older ages (data not shown). Adjusting for comorbidity did not substantially change these findings.

Subclinical hyperthyroidism and cognitive function

The study of the relationship between thyroid function and cognitive performance was focused on older participants affected by subclinical hyperthyroidism, which was the most prevalent thyroid function abnormality in our study population (Table 2). Adjusting for age, sex and other potential confounders, MMSE score was significantly lower in subclinically hyperthyroid than in euthyroid participants (22.61 ± 6.88 vs 24.72 ± 4.52 $P<.03$). In multivariate regression analysis adjusted for multiple confounders, the likelihood of having cognitive impairment associated with subclinical hyperthyroidism vs euthyroidism was 2.26 (95% CI: 1.32-3.91) and was highly significant (P=.003) (Table 3).

DISCUSSION

Using data from a representative population dispersed over a wide age-range, we found that the prevalence of subclinical hypothyroidism was 0.4% and 3%, respectively, below and above 65 years of age. In parallel, 2% of the younger and 8% of the older participants had subclinical hyperthyroidism. Consistent with other studies, we found that the prevalence of overt thyroid dysfunction in both age groups was much lower (1,2,4,15,16). Of note, the prevalences of both subclinical and overt hyperthyroidism estimated in the present study were similar to those observed in populations who live in mildly to moderately iodine

deficient areas (5,17). A recent study conducted in the US population suggests that TSH tends to increase with age, revealing a tendency toward the development of subclinical hypothyroidism (18). Interestingly, we did not confirm this finding and, almost unexpectedly, in our study TSH was slightly, but significantly, lower in older individuals. Whether the discrepancies among these studies could be explained by differences in iodine sufficiency between the US and Italy remains unclear and requires further investigation.

A slight, though significant, age-related decrease in both TSH and FT3 and an increase in FT4 plasma concentrations were found in study participants with “normal” thyroid function. One previous study conducted in 172 healthy Italian individuals aged 25 to 110 years reported that FT3 and TSH decline with age, whereas FT4 levels remain relatively stable (19). In the present, larger, population-based study, the age-related trends in TSH and FT3 were confirmed, though, contrary to the above report, we found a slight, though statistically significant, age-related increase in FT4 levels. Concomitant divergent changes in both FT3 and FT4 suggest that hepatic 5’ deiodinase activity may decline with age in humans, analogous to what has been reported in rats (20), resulting in decreased peripheral T4 degradation. The age-related decline in TSH concentrations observed in this study may be accounted for, at least in part, by a reduction in TSH secretion from the pituitary (1,21). Beyond the speculative value of these observations, it is important to note that the age-related differences in both thyroid hormone and TSH concentrations that we found in our study are subtle and unlikely to be clinically relevant. In addition, it is possible that the effect of age on thyroid dysfunction is mediated by the increased burden of comorbidity in aged individuals, which could not be fully accounted for in our analysis.

We found that subclinical hyperthyroidism was associated with impaired cognition, as measured by MMSE, even when the analysis was adjusted for potential confounders, such as chronic heart failure, smoking, and physical activity, which are known to affect cognition (22,23). An increased risk of dementia in subjects affected by subclinical hyperthyroidism was previously demonstrated in Rotterdam Study (10). In contrast, other reports have failed to demonstrate any association between thyroid dysfunction and cognition in cross-sectional or in longitudinal observations (3,8). Of note, the prevalence of subclinical hyperthyroidism observed in the negative studies was substantially lower than that observed in our study population.

The mechanism by which subclinical hyperthyroidism negatively affects cognitive function remains uncertain. Autoimmune thyroid disorders are highly prevalent among Alzheimer’s disease patients (24,25), and a significant association between autoimmune-associated subclinical hyperthyroidism and the risk of dementia has been observed (11). Data on circulating antithyroid antibodies are not available in the present study. Therefore, it cannot be excluded that thyroid autoimmunity, independently of thyroid function, may play a role in the impairment of cognitive function we observed in subclinically hyperthyroid elderly subjects. Since the population examined in this study resides in an area that is generally considered moderately iodine deficient (26,27), it can be speculated that a significant proportion of subclinically hyperthyroid subjects of this population may be affected by thyroid nodular disease and associated thyrotoxicosis. Elevated thyroid hormones tend to increase oxidative stress (28) and eventually trigger apoptosis that may lead to neuronal damage and even neuronal death (29). In addition, a hyperthyroidism-induced reduction in TRH secretion may lead to an impairment of brain acetylcholine metabolism, since TRH has been shown to increase local acetylcholine synthesis and release (30). Interestingly, in the present study, the magnitude of the odds of having decreased cognitive function were greater for subclinical hyperthyroidism than for stroke, diabetes, and Parkinson’s disease. Although our study cannot directly address this question, we speculate that high levels of

thyroid hormones may have a two-fold negative effect on neuronal cells, namely a direct metabolic damage and a signalling damage due to impairment of acetylcholine release.

In conclusion, using data from a large, population-based study, we found that the overall prevalence of thyroid dysfunction tends to be higher in older than in younger persons, with subclinical hyperthyroidism being the most highly prevalent condition. In euthyroid individuals, thyroid hormones showed significant age-related trajectories, which were small in size and unlikely to be clinically relevant. Finally, in the older population we found an independent association between subclinical hyperthyroidism and cognitive impairment. The external validity of this finding and its extension to a younger population should be tested in prospective studies and in representative populations over a wide age-range

Since subclinical hyperthyroidism can be easily reversed with treatment, unlike many of the established risk factors for cognitive decline, future studies should examine the potential cognitive benefits of treating subclinical hyperthyroidism in the elderly.

Acknowledgments

Funding sources Supported as a “target project” (ICS 110.1|RS97.71) by the Italian Ministry of Health and, in part, by the U.S. National Institute on Aging (contracts 263_MD_9164_13 and 263_MD_821336), and by grant n. FIL0774249 from MURST, Rome (to G.C.)

References

1. Mariotti S, Franceschi C, Cossarizza A, et al. The aging thyroid. Endocrine Rev. 1995; 16:686–715. [PubMed: 8747831]
2. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000; 160:526–534. [PubMed: 10695693]
3. Roberts LM, Pattison H, Roalfe A, et al. Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? Ann Intern Med. 2006; 145:573–581. [PubMed: 17043339]
4. Wilson S, Parle JV, Roberts LM, et al. Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: A community-based cross-sectional survey. J Clin Endocrinol Metab. 2006; 91:4809–4816. [PubMed: 17003083]
5. Aghini-Lombardi F, Antonangeli L, Martino E, et al. The spectrum of thyroid disorders in an iodine-deficient community: The Pescopagano survay. J Clin Endocrinol Metab. 1999; 84:561–566. [PubMed: 10022416]
6. Cooper DS. Subclinical thyroid disease: consensus or conundrum? Clin Endocrinol. 2004; 60:410–412.
7. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease. JAMA. 2004; 291:228–238. [PubMed: 14722150]
8. Gussekloo J, van Exel E, de Craen AJM, et al. Thyroid status, disability and cognitive function, and survival in old age. JAMA. 2004; 292:2591–2599. [PubMed: 15572717]
9. Jorde R, Waterloo K, Storhaugh H, et al. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endocrinol Metab. 2006; 91:145–153. [PubMed: 16263815]
10. Kalmijn S, Mehta KM, Pols HAP, et al. Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. Clin Endocrinol. 2000; 53:733–737.
11. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems contributing to the decline in ability to walk: Bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. J Am Geriatr Soc. 2000; 48:1618–1625. [PubMed: 11129752]
12. Baddeley, AD. Working Memory. Oxford, England: Clarendon Press; 1986.

13. Pisani P, Faggiano F, Krogh V, et al. Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC centers. Int J Epidemiol. 1997; 26(suppl 1):S152–S160. [PubMed: 9126543]

14. Guralnik, JM.; Fried, LP.; Simonsick, EM., et al. The Women's Health and Aging Study: Health and Social Characteristics of Older Women with Disability. NIH Publication No. 95-4009. Bethesda, MD: National Institute on Aging; 1995.

15. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survay (NHANES III). J Clin Endocrinol Metab. 2002; 87:489–499. [PubMed: 11836274]

16. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA. 2006; 295:1033–1041. [PubMed: 16507804]

17. Cavaliere R, Antonangeli L, Vitti P, et al. The aging thyroid in a mild to moderate iodine deficient area of Italy. J Endocrinol Invest. 2002; 25(10 Suppl):66–68. [PubMed: 12508922]

18. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the U.S. population: Implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007; 92:4575–4582. [PubMed: 17911171]

19. Mariotti S, Barbesino G, Caturegli P, et al. Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Metab. 1993; 77:1130–1134. [PubMed: 8077303]

20. Donda A, Lemarchand-Bérau T. Aging alters the activity of 5' deiodinase in the adenohypophysis, thyroid gland, and liver of the male rat. Endocrinology. 1989; 124:1305–1309. [PubMed: 2917513]

21. Olsson T, Viitanen M, Hagg E, et al. Hormones in 'young' and 'old' elderly: pituitary-thyroid and pituitary-adrenal axes. Gerontology. 1989; 35:144–152. [PubMed: 2792782]

22. Reitz C, den Heijer T, van Duijn C, et al. Relation between smoking and risk of dementia and Alzheimer disease: The Rotterdam Study. Neurology. 2007 Sep 4.69:998–1005. [PubMed: 17785668]

23. Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Bianchin M, Dalmonte E. Physical activity and dementia risk in the elderly: findings from a prospective Italian study. Neurology. 2008 May 6; 70(19 Pt 2):1786–94. [PubMed: 18094335]

24. Ewins DL, Rossor MN, Butler J, et al. Association between autoimmune thyroid disease and familial Alzheimer's disease. Clin Endocrinol. 1991; 35:93–96.

25. Lopez OL, Rabin BS, Huff FJ, et al. Serum autoantibodies in patients with Alzheimer's disease and vascular dementia and in nondemented control subjects. Stroke. 1992; 23:1078–1083. [PubMed: 1636181]

26. Aghini-Lombardi F, Antonangeli L, Pinchera A, et al. Effect of iodized salt on thyroid volume of children living in an area previously characterized by moderate iodine deficiency. J Clin Endocrinol Metab. 1997; 82:1136–1139. [PubMed: 9100585]

27. Aghini-Lombardi FA, Pinchera A, Antonangeli L, et al. Mild iodine deficiency during fetal/neonatal life and neuropsychological impairment in Tuscany. J Endocrinol Invest. 1995; 18:57–62. [PubMed: 7759786]

28. Videla LA, Sir T, Wolff C. Increased lipid peroxidation in hyperthyroid patients: Suppression by propylthiouracil treatment. Free Radic Res Commun. 1988; 5:1–10. [PubMed: 3234861]

29. Chan RS, Huey ED, Maecker HL, et al. Endocrine modulators of necrotic neuron death. Brain Pathol. 1996; 6:481–491. [PubMed: 8944318]

30. Kinoshita K, Kawashima K, Kawashima Y, et al. Effect of TA-0910, a novel thyrotropin-releasing hormone analog, on in vivo acetylcholine release and turnover in rat brain. Jpn J Pharmacol. 1996; 71:139–145. [PubMed: 8835640]

Table 1

Characteristics of participants younger than 65 years

	n=1	n=1	n=243	n=5	n=5	
	Overt Hypothyroidism	**Subclinical Hypothyroidism**	**Euthyroidism**	**Subclinical Hyperthyroidism**	**Overt Hyperthyroidism**	***p****
Age (years) #	62.52	38.73	44.35 ± 13.02	47.64 ± 16.20	39.68 ± 16.08	*0.52*
Sex female (%)	100	0	53.91	80.00	60.00	*0.77*
Education (years) #	5.0	14.0	10.78 ± 4.47	7.80 ± 3.56	11.60 ± 5.36	*0.82*
Mini-Mental State Examination corrected score (0-30)#	29.00	29.00	28.36 ± 1.82	28.20 ± 2.05	29.40 ± 0.89	*0.52*
TSH (mUI/L) #	50.3	5.26	1.71 ± 0.80	0.40 ± 0.04	0.16 ± 0.12	*<.0001*
FT4 (ng/dL) #	0.64	0.87	1.33 ± 0.24	1.21 ± 0.12	2.45 ± 0.29	*<.0001*
FT3 (pg/mL) #	2.75	3.67	4.33 ± 0.45	4.26 ± 0.56	6.31 ± 1.41	*<.0001*
Physical Activity						*0.90*
Sedentary (%)	0	0	12 (4.9)	0	0	
Light (%)	1 (100)	1 (100)	184 (75.7)	5 (100)	4 (80.0)	
Moderate/High (%)	0	0	47 (19.4)	0	1 (20.0)	
Smoking (current *vs* ever and never smoked) (n, %)	0	0	85 (35.0)	2 (40.0)	1 (20.0)	*0.89*
Heart rate (beats/minute) #	67.00	44.00	69.05 ± 11.01	71.80 ± 12.87	83.00 ± 22.27	*0.005*
Body Mass Index (kg/m^2) #	26.48	27.29	26.12 ± 4.14	23.39 ± 5.21	25.58 ± 3.55	*0.66*

*From Age- and Sex- Adjusted Linear or Logistic Regression Models as Appropriate.

#Mean ± Standard Deviation

Reference normal values:

TSH, 0.46 - 4.68 mIU/L

FT3, 2.77 - 5.27 pg/mL

FT4, 0.77 - 2.19 ng/dl

Table 2

Characteristics of participants older than 65 years

	n=5	n=25	n=800	n=71	n=15	
	Overt Hypothyroidism	**Subclinical Hypothyroidism**	**Euthyroidism**	**Subclinical Hyperthyroidism**	**Overt Hyperthyroidism**	***P****
Age (years) #	76.20 ± 8.01	77.04 ± 7.42	75.34 ± 7.31	76.05 ± 8.27	78.54 ± 7.40	*0.37*
Sex female (%)	60.00	72.00	55.25	56.34	66.67	*0.99*
Education (years) #	6.00 ± 3.46	5.60 ± 4.32	6.71 ± 5.29	4.69 ± 2.18	4.27 ± 1.48	*0.98*
Mini-Mental State Examination corrected score (0-30)#	23.80 ± 5.12	24.84 ± 3.17	24.72 ± 4.52	22.61 ± 6.88	22.53 ± 5.94	*0.002*
TSH (mUI/L) #	52.00 ± 34.63	7.99 ± 4.74	1.54 ± 0.85	0.28 ± 0.13	0.04 ± 0.07	*<.0001*
FT4 (ng/dL) #	0.51 ± 0.21	1.28 ± 0.31	1.45 ± 0.30	1.53 ± 0.30	2.48 ± 0.87	*<.0001*
FT3 (pg/mL) #	2.91 ± 0.73	4.28 ± 0.58	4.23 ± 0.44	4.32 ± 0.44	6.19 ± 2.21	*<.0001*
Physical Activity						*0.13*
Inactive/Light (%)	3 (60.0)	5 (20.0)	168 (21.0)	21 (29.6)	7 (46.7)	
Moderate (%)	2 (40.09	18 (72.0)	590 (73.8)	47 (66.2)	7 (46.7)	
Intense (%)	0	2 (8.0)	42 (5.2)	3 (4.2)	1 (6.6)	
Smoking (current *vs* ever and never smoked) (n, %)	1 (20.0)	1 (4.0)	118 (14.8)	9 (12.7)	3 (20.0)	*0.90*
Heart rate (beats/minute) #	84.00 ± 23.58	70.42 ± 12.42	69.44 ± 12.04	72.13 ± 13.32	69.92 ± 11.01	*0.99*
Body Mass Index (kg/m^2) #	33.24 ± 8.65	27.08 ± 4.79	27.27 ± 4.01	27.68 ± 4.09	26.91 ± 5.85	*0.49*

*From Age- and Sex- Adjusted Linear or Logistic Regression Models as Appropriate.

#Mean ± Standard Deviation

Reference normal values:

TSH, 0.46 - 4.68 mIU/L

FT3, 2.77 - 5.27 pg/mL

FT4, 0.77 - 2.19 ng/dl

Table 3

Multivariate regression analysis* relating subclinical hyperthyroidism to the risk of having low Mini-Mental State Examination score (< 24)

Characteristic	H.R.	95% C.I.	*P*
Subclinical Hyperthyroidism	2.26	[1.32-3.91]	0.003
Age	1.12	[1.09-1.14]	<.0001
Sex	1.62	[1.15-2.30]	0.006
Physical activity	0.64	[0.45-0.91]	0.01
Stroke	1.38	[0.99-1.90]	0.05
Parkinson's disease	2.11	[1.06-4.19]	0.03
Diabetes	1.06	[0.99-1.13]	0.06

*Also adjusted for smoking, hypertension, and chronic heart failure (using backward selection analysis)