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Thyrotropin level and cognitive performance: Baseline results from the ELSA-Brasil Study

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ABSTRACT

Background and aims: The role of subtle thyroid alterations, such as subclinical thyroid disease and low/high serum thyrotropin (TSH) within the normal range, on cognitive decline is controversial. The aim of this study was to evaluate the association of serum TSH and subclinical thyroid dysfunction with performance on cognitive tests in a large sample of Brazilian middle-aged adults without overt thyroid disease.

Methods: In this cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health, we excluded individuals aged 65 years and older, with overt thyroid dysfunction, prevalent stroke, in use of medications that affect thyroid function or that indicate neurologic diseases, and from Asian or indigenous ethnicity. Thyroid status was assessed by serum TSH and free thyroxine (only when the TSH was altered). Individuals were divided according to TSH tertiles and classified according to thyroid function as euthyroidism, subclinical hypothyroidism, or subclinical hyperthyroidism. Cognition was evaluated using delayed word recall test, semantic verbal fluency test, and trail making test version B. The associations of cognitive tests performance with TSH tertiles (using the middle tertile as reference) and thyroid function were investigated using linear regression models, adjusted for an extensive set of possible confounders (sociodemographic characteristics, cardiovascular risk factors, and depression).

Results: The mean age of the 10,362 participants was 49.5 ± 7.4 years, 52.3% women. After adjustment for confounders, the first TSH tertile was associate with worse performance on the trail making test (β = −0.05, 95% CI = −0.09; −0.01, p = 0.017). When restricting the analysis to the 9769 individuals with TSH within the normal range, the association between TSH and performance on the trail making test remained significant (β = −0.05, 95% CI = −0.09; −0.01, p = 0.020) on multiple linear regression. Subclinical thyroid disease was not associated with performance on cognitive tests.

Conclusion: Low TSH is associated with poorer performance on an executive function test in middle-aged adults without overt thyroid dysfunction.

1. Introduction

The association between cognitive decline and overt thyroid dysfunction is well known and clinical guidelines recommend dosing serum thyrotropin (TSH) when evaluating individuals with cognitive impairment (Knopman et al., 2001). However, controversies remain on the role of subtler thyroid function alterations in cognitive impairment, particularly serum TSH levels within the range of euthyroidism or subclinical thyroid disease.

Studies evaluating the association of TSH levels with dementia and cognitive impairment show conflicting results: low TSH levels associated with prevalent dementia in older adults without clinical thyroid disease (Benseñor et al., 2010), high TSH levels predicting incident dementia in older adults (Tan et al., 2008; Forti et al., 2012) and associated with poorer performance on cognitive tests (Hogervorst et al., 2008; Beydoun et al., 2012; Beydoun et al., 2013), and no association between TSH levels and incident dementia (De Jong et al., 2006) or performance on cognitive tests (Formiga et al., 2013). In the same

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manner, studies that evaluated TSH within the normal range demonstrated an association between lower baseline levels of TSH and incident mild cognitive impairment (Moon et al., 2014), between higher TSH and lower risk of dementia (Chaker et al., 2016), or no association between TSH and dementia (Tan et al., 2008; Benseñor et al., 2010) and cognitive decline (Volpato et al., 2002; Hogervorst et al., 2008; Castellano et al., 2013). On the other hand, the evidence on the relation between subclinical thyroid disease is less polemic: recent meta-analyses and systematic reviews suggest that subclinical hypothyroidism is not associated with increased risk of dementia, poor performance on cognitive tests, or cognitive decline (Akintola et al., 2015; Pasqualetti et al., 2015; Rieben et al., 2016), while subclinical hyperthyroidism is associated with dementia and cognitive impairment (Gan and Pierce, 2012; Rieben et al., 2016).

Since most of the studies were done in older adults from developed countries, little is known about the influence of TSH levels within normal or subclinical thyroid disease ranges on cognitive outcomes in normal cognitive aging among young and middle-aged adults, especially in low and middle-income countries. Thus, the aim of this study was to investigate the association of performance on cognitive tests with serum TSH and thyroid function in adults without overt thyroid dysfunction participating in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

2. Methods

2.1. Study population and design

The present study is a cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) baseline evaluation. The ELSA-Brasil is a cohort of 15,105 active and retired employees from public institutions located in different regions of Brazil (5 universities and 1 research institute), aged between 35 and 74 years, and free of dementia at enrollment. Baseline evaluation (from August 2008 to December 2010) included information on socio-demographics, clinical history, family history of diseases, lifestyle factors, mental health, cognitive status, and occupational exposure. Anthropometric measurements, and laboratory and imaging tests were also obtained. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local institutional review boards. All participants signed the informed consent prior to enrollment. Further details of the ELSA-Brasil study can be found elsewhere (Aquino et al., 2012; Schmidt et al., 2015).

For this analysis, we excluded the following participants: (1) aged 65 years and older; (2) with overt thyroid dysfunction, assessed by routine use of thyroid hormones or anti-thyroid drugs, and/or hormonal levels: TSH $>$ 4.0 mIU/l and free thyroxine (FT4) $<$ 0.9 ng/dl for overt hypothyroidism and TSH $<$ 0.4 mIU/l and FT4 $>$ 1.8 ng/dl for overt hyperthyroidism; (3) that were using medications that can alter thyroid function (amiodarone, carbamazepine, carbidopa, phenytoin, furosemide, haloperidol, heparin, levodopa, lithium, metoclopramide, propranolol, primidone, rifampicin and valproic acid); (4) that were using drugs that indicate neurologic or psychiatric disease, or could directly interfere with performance on cognitive tests, such as neuroleptics, antiparkinsonian agents, and anticonvulsants; (5) with self-reported diagnosis of stroke to minimize the effect of previous cerebrovascular disease on cognitive function; (6) from Asian or indigenous ethnicities because of their low proportion in the sample; (7) with incomplete data for TSH levels, thyroid function, cognitive tests, and other covariates used to adjust for confounders.

2.2. Thyrotropin assessment

Venous blood samples were obtained following an overnight fast. After centrifugation, the serum was used for hormone analysis. TSH and FT4 were measured by a third generation immunoenzymatic assay (Centaur Siemens®, Germany); however, FT4 was only measured in participants with altered TSH levels. Participants were divided in groups according to TSH tertiles and were classified according to TSH, FT4 (if TSH was altered) and information on medication use for treatment of thyroid disorders as follows: subclinical hypothyroidism (TSH $>$ 4.0 mIU/l, FT4 between 0.9 and 1.8 ng/dl, and no routine medicine use for thyroid disorder), subclinical hyperthyroidism (TSH $<$ 0.4 mIU/l, FT4 between 0.9 and 1.8 ng/dl, and no routine medicine use for thyroid disorder), and euthyroidism (normal TSH and no medicine use for thyroid disorder). Cutoff values of TSH and FT4 were similar to those used in the National Health and Nutritional Examination Survey (NHANES III) and recommended by Surks et al. (2004).

2.3. Assessment of cognitive function

We used three neuropsychological tests administered by trained examiners in a fixed order, during a single session in a quiet room, with good lighting and low noise level (Passos et al., 2014). From the Brazilian version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), the delayed word recall test evaluates verbal learning and recent memory. Ten unrelated printed words were shown to participants in three learning trials. After a five-minute delay, participants were given 60 s to recall the words. The score corresponded to the number of recalled words (Morris et al., 1989; Bertolucci et al., 2001). The semantic verbal fluency test evaluates language and executive function by asking participants to name as many animals as possible in 60 s. The score corresponded to the total number of given words (Jones et al., 2006). Finally, the trail making test version B assesses executive function, processing speed, and visuospatial ability. Participants were instructed to draw lines connecting numbers to letters in an order that alternated between the increasing numeric value and the alphabetic order. The test score was the total time taken to complete the task, in seconds (Greenlief et al., 1985).

2.4. Assessment of covariates

Information regarding potential confounders were also obtained at the baseline evaluation (Aquino et al., 2012; Schmidt et al., 2015). Sociodemographic data were age, sex, race (white vs mixed or black), and schooling (middle school or lower vs high school or higher). Cardiovascular risk factors evaluated were hypertension (use of anti-hypertensive drug, systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg), diabetes mellitus (self-reported, use of oral hypoglycemic agents or insulin therapy, fasting plasma glucose $\geq$ 126 mg/dl, 2-h post-prandial 75 g glucose test $\geq$ 200 mg/dl, or glycosylated hemoglobin $\geq$ 6.5%), low density lipoprotein cholesterol (calculated using the Friedewald equation) (Fedeli et al., 2013), coronary artery disease (previous self-reported myocardial infarction or myocardial revascularization), previous self-reported heart failure, current smoking status, current alcohol use, and moderate or intense leisure time physical activity. Depression was assessed by the Clinical Interview Scheduled Revised (Botega et al., 1995).

2.5. Statistical analysis

Data are presented as mean ± standard deviation (SD) for continuous variables with normal distribution; as median and interquartile range (IQR) for non-normally distributed continuous variables; and as number and frequency for categorical variables. Characteristics of participants according to TSH tertile and thyroid function were compared using one-way ANOVA, Kruskall-Wallis test, Chi-square test, and Fisher's exact test for continuous variables with normal distribution, non-normally distributed continuous variables, categorical variables, and categorical variables with small cell counts, respectively.

For all participants, the raw scores on the cognitive tests were