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ORIGINAL ARTICLE

Subclinical thyroid dysfunction and psychiatric disorders: cross-sectional results from the Brazilian Study of Adult Health (ELSA-Brasil)

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Summary

Objective To evaluate the association between subclinical thyroid dysfunction and psychiatric disorders using baseline data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

Design Cross-sectional study.

Patients The study included 12 437 participants from the ELSA-Brasil with normal thyroid function (92·8%), 193 (1·4%) with subclinical hyperthyroidism and 784 (5·8%) with subclinical hypothyroidism, totalling 13 414 participants (50·6% of women).

Measurements The mental health diagnoses of participants were assessed by trained raters using the Clinical Interview Schedule – Revised (CIS-R) and grouped according to the International Classification of Diseases 10 (ICD-10). Thyroid dysfunction was assessed using TSH and FT4 as well as routine use of thyroid hormones or antithyroid medications. Logistic models were presented using psychiatric disorders as the dependent variable and subclinical thyroid disorders as the independent variable. All logistic models were corrected for multiple comparisons using Bonferroni correction.

Results After multivariate adjustment for possible confounders, we found a direct association between subclinical hyperthyroidism and panic disorder odds ratio [OR], 2·55; 95% confidence Interval (95% CI), 1·09–5·94; and an inverse association between subclinical hypothyroidism and generalized anxiety disorder (OR, 0·75; 95% CI, 0·59–0·96). However, both lost significance after correction for multiple comparisons.

Conclusion Subclinical hyperthyroidism was positively associated with panic disorder and negatively associated with anxiety disorder, although not significant after adjustment for multiple comparisons.

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Introduction

Thyroid dysfunction and psychiatric disorders are common in the general population.[1,2] Although it is common to associate hypothyroidism with depression and hyperthyroidism with anxiety in clinical practice, mixed results have been reported regarding these associations and some potential confounders could play an important role.[3] For instance, Forman-Hoffman *et al.*, in the Third National Health and Nutrition Examination Survey (NHANES), a population-based study that examined 6869 subjects aged 17–39 years found that lower thyroid stimulating hormone (TSH) and higher thyroxine (T4) levels were associated with depression in men, while only free-thyroxine (FT4) levels correlated with depression in women.[4] Roberts *et al.*, in the Birmingham Elderly Thyroid Study, a community-based study, of 5960 participants found no association between subclinical thyroid diseases and depression or anxiety.[5] De Jongh *et al.*, in the Longitudinal Aging Study Amsterdam (LASA), found no association between subclinical hypothyroidism and depression in 1219 participants aged ≥65 years.[6] Engum *et al.* also reported no association between subclinical thyroid disorder and psychiatric symptoms in 30 589 individuals aged 40–89 years in the HUNT study.[7] In contrast, Grabe *et al.*, in 3790 participants of the Study of Health in Pomerania (SHIP) found an association between overt hyperthyroidism and improved self-rated mental and physical health.[8] Finally, Panicker *et al.* studied 33 234 participants from the HUNT Study, treated or not treated for thyroid diseases. In males not on T4, there were 11% fewer depression cases per mIU/l increase in TSH and 19% less anxiety cases. However, for women not on T4, there was no association

with depression and a trend towards a small inverse relationship with anxiety (4% less anxiety cases per mIU/l increase in TSH).[9]

Two other studies, with patients referred from specialized clinics, also reported conflicting results. Larish *et al.*, using the General Health Questionnaire (GHQ 12) in patients with overt and subclinical thyroid dysfunction, found only overt hypothyroidism was associated with depressive symptoms.[10] Gulseren *et al.* evaluated the presence of depression and anxiety using the Hamilton Depression and Anxiety Rate scales in patients with subclinical and clinical hypothyroidism and hyperthyroidism. Compared to the control group, patients with subclinical thyroid dysfunction had higher scores for both depression and anxiety, although not as high as those with overt thyroid disorders.[11]

These studies showed mixed results regarding the association between psychiatric disorders and thyroid function. However, the designs of these studies were very heterogeneous. For instance, there were population-based studies,[4] community-based studies[5–7] and studies that selected participants from specialized clinics or tertiary care facilities.[10] Psychiatric diagnoses were made using different instruments.[4,11,12] Finally, although most studies evaluated the association of psychiatric disorders with depression[4–6,12–14] only a few also investigated anxiety disorders.[7,9–11]

Therefore, we aimed to investigate the association between subclinical thyroid dysfunction and psychiatric disorders by analysing cross-sectional data from the baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), a multicentre cohort study conducted in six different cities in Brazil. Given the large sample of the ELSA-Brasil and the high prevalence of thyroid[15,16] and psychiatric disorders in Brazil,[17,18] our setting is particularly suitable to explore this putative association.

Methods

The ELSA-Brasil study has been described previously. Briefly, 15 105 civil servants aged from 35 to 74 years old and from six cities in Brazil (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, Sao Paulo and Vitoria) were enrolled between August 2008 and December 2010.[19–21] ELSA-Brasil is not a population-based study, and the sample is not representative of the Brazilian population. All active or retired employees of the six institutions aged 35–74 years were eligible for the study. Exclusion criteria were current or recent (<4 months prior to the first interview) pregnancy, intention to quit working at the institution in the near future, severe cognitive or communication impairment, and, if retired, residence outside of a study centre's corresponding metropolitan area. Compared to the Brazilian general population, ELSA-Brasil participants had higher net family income, higher levels of educational attainment and more access to health care. However, they were selected according to study goals including a similar number of participants with occupation classified as unskilled, technical/clerical and faculty and professional staff permitting a gradient of socio-economic position across the sample. Although race/skin colour was not equally distributed as in the Brazilian census, it reflects the population characteristics of the country. The ELSA-Brasil protocol was approved at all six centres by the Institutional Review Boards addressing research in human participants. All participants provided informed consent.

As measured by self-rated race/colour using the same question used in the Brazilian census 2010, 52% of participants were white, 28% were pardos ('browns' or of mixed colour), 16% were black, 3% were Asian (mainly Japanese Brazilians), and 1% were indigenous.

Data collection

Each participant underwent an interview at their workplace and visited the Research Centre for another interview and clinical examination, according to standard protocols developed for the study.[22] The interview and examination at each site were conducted under strict quality control. The questionnaire addressed socio-demographic factors, the level of formal education, income, race/skin colour, marital status and smoking status. The highest level of education was categorized as less than high school, high school and college; monthly income was a continuous variable; and race/skin colour was self-reported as one of five categories: White, Brown, Black, Asian and Indigenous using the same question used in Brazilian census. Marital status was defined as single or not single. Smoking status was defined as never, former and current smoker. Alcohol consumption was defined as never, past and current. All participants were asked about their use of regular and over-the-counter medicines in the last 15 days including benzodiazepines and antidepressants.

Common psychiatric disorders

Mental health diagnoses were assessed by trained raters using the validated, Portuguese version of the Clinical Interview Schedule – Revised (CIS-R). The CIS-R is a structured interview for the measurement and diagnosis of nonpsychotic psychiatric morbidity in the community. This short and straightforward questionnaire was developed in 1992 by Lewis *et al.* to be used specifically in the community and primary care.[23] Importantly, lay interviewers are as reliable as psychiatrists in using the CIS-R for performing mental health diagnoses; thus, it is a suitable instrument to be used in epidemiological studies. The complete CIS-R version includes 14 sections covering symptoms of depression and anxiety, obsessions, compulsions, panic, phobias, anxiety and worries, including worry about physical health, depression, depressive ideas, irritability, fatigue, concentration, sleep and somatic symptoms.

Specific disorders were diagnosed by applying algorithms based on the ICD-10 diagnostic criteria for research to examination answers for various sections of the CIS-R (World Health Organization, 2010).[24] According to Lewis, six diagnostic categories can be obtained from the CIS-R: anxiety disorders (GAD, F41·1), depressive episodes (MDD, F32.xx), all phobias (F40·2), obsessive-compulsive disorder (F42) and panic disorder (F41·0). Additionally, a diagnosis of a mixed anxiety and depressive disorder (MADD, F41·2) can be made when a subject with common mental disorder CMD (i.e. CIS-R>12) does not fulfil

the criteria for any of these five ICD-10 diagnostic categories (Lewis *et al.*). The questionnaire was translated and adapted to Brazilian Portuguese.[25]

In the cross-cultural adaptation of the CIS-R to Brazilian Portuguese especially for the study, we used a universalist approach as proposed by Herdman *et al.* focused in the future use of the questionnaire in all Brazilian regions.[26]

Thyroid function

Venous blood samples were obtained after an overnight fast. The serum obtained after centrifugation was used for hormone and biochemistry measurements. The TSH and FT4 were measured by a third generation immunoenzymatic assay (Siemens). Thyroid dysfunction was assessed using TSH and FT4 levels and routine use of thyroid hormones or antithyroid medications, such as propylthiouracil or methimazole. However, FT4 levels were only evaluated in participants who presented with altered TSH levels. Therefore, if TSH levels were normal, FT4 levels were not obtained. The cut-off levels for TSH were <0·4 mIU/l for hyperthyroidism and >4·0 mIU/l for hypothyroidism. Cut-off levels for FT4 were <10·3 pmol/l for hypothyroidism and >24·5 pmol/l for hyperthyroidism. Cut-off values for TSH and FT4 were similar to those used in the National Health and Nutritional Examination Survey (NHANES) III[27] and recommended by Surks with no correction for age.[28] However, all multivariate analyses were adjusted for age. Participants in the sample were classified into five categories according to TSH and FT4 (if TSH was altered) levels, and information regarding the use of medication for treatment of thyroid disorders: clinical hyperthyroidism (low serum TSH and high levels of FT4 or use of medication for treatment of hyperthyroidism), subclinical hyperthyroidism (low serum TSH, normal levels of FT4 and no use of medication for treatment of thyroid diseases), euthyroidism (normal TSH and no use of medication to treat thyroid diseases), subclinical hypothyroidism (high TSH levels, normal levels of FT4, and no use of medication for treatment of hypothyroidism), and clinical hypothyroidism (high TSH and low FT4 levels or use of levothyroxine for treatment of hypothyroidism). We excluded participants using other drugs that can interfere with thyroid function, such as: amiodarone, carbamazepine, carbidopa, phenytoin, furosemide, haloperidol, heparin, levodopa, lithium, metoclopramide, propranolol, primidone, rifampicin and valproic acid.[29,30]

Statistical analysis

Categorical variables are presented as proportions and compared using chi-square or Fisher's exact test, as appropriate. Continuous variables are presented as the mean (standard deviation) and compared using ANOVA. Subclinical hyperthyroidism and hypothyroidism were analysed separately using normal thyroid function as the reference. Logistic regression models using the diagnosis of each psychiatric disorder as the dependent variable and the subclinical thyroid dysfunction (subclinical hyperthyroidism or subclinical hypothyroidism) as the independent variable were built with respective 95% confidence intervals (95% CI). In multivariate analysis, we included all variables with a $P < 0{\cdot}20$ in Table 1. For subclinical hyperthyroidism, selected variables were as follows: age, gender, race, marital status, mean of monthly income and smoking; for subclinical hypothyroidism, selected variables were as follows: age, race, education, marital status, mean of monthly income, smoking and alcohol use. Crude models are presented as well as those adjusted for age and sex (Model 1 for subclinical hyperthyroidism) and only age (model 1 for subclinical hypothyroidism), and those with multivariate adjustment (Model 2). All logistic models were corrected for multiple comparisons using Bonferroni correction. All analyses were carried out using Statistical Package for Social Sciences (SPSS) version 22.0. The level of significance was set at 0·05.

Results

Of the 15 105 participants, 17 had missing values for TSH, FT4; 19 had missing values for use of medication to treat thyroid diseases; 9 presented with low but near normal TSH values and FT4 levels, suggesting central hypothyroidism; and four used levothyroxine and methimazole at the same time. All of these subjects were excluded from the analysis, resulting in 15 056 eligible participants. Of these, 466 who used medications that can alter thyroid function or interfere with TSH and FT4 tests and 1176 with overt thyroid disease were also excluded from the analysis, leaving 13 414 participants. Table 1 shows the general characteristics of the sample. Subjects with subclinical hyperthyroidism less frequently had white skin colour and had a higher frequency of current smokers and panic disorder compared to euthyroid participants. Subjects with subclinical hypothyroidism more frequently had white skin colour, and less frequently were current smokers and reported alcohol consumption or had generalized anxiety disorders, compared to euthyroid subjects.

As there was no difference in the results according to gender, all analyses are presented for the whole sample. For subjects with subclinical hyperthyroidism, there was a positive association with panic disorder (OR, 2·55; 95% CI, 1·09–5·94) while participants with subclinical hypothyroidism had an inverse association with generalized anxiety disorder (OR, 0·75; 95% CI, 0·59–0·96). After Bonferroni correction for multiple comparisons, both associations lost significance (Table 2).

We also found a possible association of subclinical hyperthyroidism and hypothyroidism with major depressive disorder. Although suggestive, the ORs were not statistically significant, either for subclinical hyperthyroidism (OR 1·44; 95% CI, 0·79–2·62) or for subclinical hypothyroidism (OR, 1·31; 95% CI, 0·94–1·83).

Discussion

Our results showed a significant association between subclinical hyperthyroidism and panic disorder after multivariate adjustment for possible confounders. However, this association lost significance after correction for multiple comparisons. Some previous studies with small samples detected alterations of the hypothalamic–pituitary–thyroid axis in cases of panic

Table 1. General characteristics of the sample, according to type of thyroid dysfunction

	Euthyroidism n = 12 437	Subclinical Hyperthyroidism n = 193	P†	Subclinical Hypothyroidism n = 784	P‡
TSH mIU/l*	1·67 (0·81)	0·25 (0·12)	<0·0001	7·07 (14·38)	<0·0001
Free-T4 pmol/l*§		16·0 (3·0)		14·2 (2·3)	
Age (years)*	51·5 (9·0)	53·3 (9·1)	0·007	54·1 (9·1)	<0·0001
Women (%)	6426 (51·7)	123 (63·7)	0·001	423 (54)	0·21
Race (%)					
White	6276 (51·1)	72 (38·1)	<0·0001	474 (61)	<0·0001
Brown	3549 (28·9)	54 (28·6)		207 (26·6)	
Black	2029 (16·5)	54 (28·6)		70 (9)	
Asian	311 (2·5)	8 (4·2)		16 (2·1)	
Indigenous	127 (1)	1 (0·5)		10 (1·3)	
Education (%)					
Below HS	1559 (12·5)	30 (15·5)	0·30	116 (14·8)	0·17
High School (HS)	4351 (35)	71 (36·8)		272 (34·7)	
College	6527 (52·5)	92 (47·7)		396 (50·5)	
Not single	8384 (67·4)	118 (61·1)	0·07	477 (60·8)	<0·0001
Mean monthly income (%)	1715 (1406)	1529 (1213)	0·07	1850 (1650)	0·01
Self-reported health status (%)					
Very good	3606 (29)	61 (31·6)	0·10	215 (27·4)	0·86
Good	6483 (52·1)	86 (44·6)		423 (54)	
Regular	2123 (17·1)	40 (20·7)		132 (16·8)	
Bad	184 (1·5)	4 (2·1)		11 (1·4)	
Very bad	37 (0·3)	2 (1)		3 (0·4)	
Major depressive disorder (%)	496 (4)	12 (6·2)	0·12	40 (5·1)	0·13
Generalized anxiety disorders (%)	1613 (13·1)	24 (12·6)	0·85	78 (10)	0·01
Panic disorder (%)	122 (1)	6 (3·1)	0·003	4 (0·5)	0·19
Mixed anxiety and depression disorder (%)	1571 (12·6)	23 (11·9)	0·77	90 (11·5)	0·34
Obsessive-compulsive disorder (%)	262 (2·1)	5 (2·6)	0·65	16 (2)	0·90
Common mental disorder (%)	3286 (26·4)	54 (28)	0·63	186 (23·7)	0·10
Total score	8·1 (7·9)	8·7 (8·6)	0·35	7·5 (7·8)	0·02
Smoking (%)					
Never	7114 (57·2)	91 (47·2)	0·008	437 (55·7)	<0·0001
Past	3638 (29·3)	64 (33·2)		273 (34·8)	
Current	1684 (13·5)	38 (19·7)		74 (9·4)	
Alcohol use (%)					
Never	1260 (10·1)	26 (13·5)	0·22	103 (13·1)	0·03
Past	2430 (19·6)	41 (21·2)		148 (18·9)	
Current	8733 (70·3)	126 (65·3)		533 (68)	
Use of benzodiazepines	405 (3·3)	7 (3·6)	0·77	30 (3·8)	0·39
Use of antidepressants	743 (6)	13 (6·7)	0·66	55 (7)	0·24

*Values represent the mean (standard deviation).
†P values for comparison between euthyroidism and subclinical hyperthyroidism.
‡P values for comparison between euthyroidism and subclinical hypothyroidism.
§As FT4 mean values were only tested if TSH was altered, and only a small number of participants has FT4 values if TSH levels were normal, we cannot present FT4 levels for all 12 437 euthyroid participants.

disorder.[31–35] Two studies reported a diminished TSH response to thyrotropin-releasing hormone (TRH) stimulation.[31,32] Yeragani *et al.* detected a great variability in T4 levels in patients with panic disorders compared to controls.[33] Kikuchi *et al.* found higher TSH concentrations in patients with severe attacks of panic compared to patients with mild and moderate attacks.[34] Fardellas reported that hypothyroidism was more frequent in patients with mood disorders and hyperthyroidism in patients with panic disorder in a sample of 268 patients.[35] Although the association between panic disorder and subclinical hyperthyroidism in our sample lost significance after correction for multiple comparisons, we have the possibility to analyse data prospectively in the near future. Interestingly, in another cohort in Brazil, we found an association between subclinical hyperthyroidism and dementia in a cross-sectional analysis of people ≥65 years old in a poor neighbourhood of São Paulo.[36] These findings, together with the results of this study, could suggest that subclinical hyperthyroidism may be associated with psychiatric disorders and dementia in the Brazilian population.

Table 2. Odds ratio (OR) and 95% confidence interval (95% CI) for the association between psychiatric disorders and subclinical hyperthyroidism and subclinical hypothyroidism using euthyroidism as reference

	Subclinical hyperthyroidism		
	Crude	Model 1	Model 2
Major depressive disorder	1·60 (0·88–2·88)	1·50 (0·83–2·71)	1·44 (0·79–2·62)
Anxiety disorder	0·96 (0·62–1·48)	0·90 (0·58–1·39)	0·88 (0·57–1·37)
Panic disorder	3·24 (1·41–7·44)*	3·08 (1·34–7·09)*	2·55 (1·09–5·94)*
Obsessive-compulsive disorder	1·23 (0·50–3·03)	1·21 (0·49–2·97)	1·18 (0·48–2·90)
Mixed anxiety and depressive disorder	0·94 (0·60–1·45)	0·91 (0·59–1·42)	0·85 (0·54–1·34)
Common mental disorder	1·08 (0·79–1·48)	1·03 (0·75–1·43)	0·97 (0·70–1·35)
	Subclinical hypothyroidism		
	Crude	Model 1	Model 2
Major depressive disorder	1·29 (0·93–1·80)	1·35 (0·97–1·88)	1·31 (0·94–1·83)
Anxiety disorder	0·74 (0·58–0·94)*	0·77 (0·61–0·98)*	0·75 (0·59–0·96)*
Panic disorder	0·52 (0·19–1·40)	0·50 (0·19–1·37)*	0·52 (0·19–1·42)*
Obsessive-compulsive disorder	0·97 (0·58–1·61)	1·03 (0·62–1·71)	0·98 (0·59–1·64)
Mixed anxiety and depressive disorder	0·90 (0·72–1·12)	0·95 (0·75–1·19)	0·94 (0·75–1·19)
Common mental disorders	0·87 (0·73–1·03)	0·92 (0·78–1·09)	0·90 (0·76–1·08)

Model 1: adjusted by age and gender for subclinical hyperthyroidism and only age for subclinical hypothyroidism; Model 2: multivariate adjustment.
*OR (95% CI) lost significance after correction for multiple comparisons.

Our analysis detected a possible protective effect of subclinical hypothyroidism for anxiety disorder. Panicker *et al.* reported a trend towards a low inverse relationship with anxiety: 19% less anxiety cases per mIU/l increase in TSH in men and a trend to less anxiety in women, both not using thyroxine in the HUNT Study.[8] Grabe *et al.* found an association between overt hyperthyroidism and distressing mental symptoms, but no association was reported for subclinical hyperthyroidism.[7]

Our results for subclinical hypothyroidism suggest an association with depression although this was not statistically significant. A previous population-based study in the city of Rio de Janeiro, Brazil, found a positive association between subclinical hypothyroidism and depressive symptoms in women with TSH levels higher than 10 mIU/l.[37] ELSA-Brasil included a high number of men compared to the Guimarães study that only included women. Three other studies in Brazil reported a positive association between subclinical hypothyroidism and psychiatric symptoms and depression. However, all of them included only a small number of patients, mainly women referred to specialized clinics.[38–40] Differences in the population selected and in the total size of the sample could partially explain the little differences in results.

We also evaluated the association between perceived health status and thyroid disease. One previous study evaluated perceived health status in 232 women with overt hypothyroidism or subclinical hypothyroidism, and euthyroid controls using Short Form 36 (SF-36). Patients with overt thyroid disease presented lower scores when compared to subclinical hypothyroidism and controls; in addition, women with subclinical hypothyroidism presented intermediate score values that fell between values from women with overt disease and controls.[41] In our sample, we evaluated perceived health status with only one question. We did not find any association between subclinical hypothyroidism and perceived health status, and our results suggest it is more likely that any association would be with subclinical hyperthyroidism ($P = 0{\cdot}10$).

Although some studies detected alterations of the hypothalamic–pituitary–thyroid axis in subjects with psychiatric disorders and especially with panic disorder, the results were not homogeneous. Our measure of thyroid function using TSH, FT4 and use of medication to treat thyroid diseases is independent of the psychiatric diagnosis (CIS-R), but this is a cross-sectional analysis and we need information from prospective studies to evaluate causality. Regarding biological plausibility, Hamilton *et al.* previously suggested that there are genes on chromosome 13q that could be associated with a syndrome characterized by panic disorder, bladder problems, mitral valve prolapse and thyroid disorders.[42] However, no further data were reported to confirm these results.

Our results confirmed previous data that showed a higher frequency of smoking in patients with subclinical hyperthyroidism and a lower frequency in patients with subclinical hypothyroidism.[43] There was also an inverse association between current alcohol use and presence of subclinical thyroid disorders, although this was only statistically significant for subclinical hypothyroidism.[44]

Our study has several methodological strengths, notably its large sample size and multicentre nature. We also collected psychiatric data using CIS-R, a very reliable and standardized tool for diagnosing depressive and anxiety disorders. The CIS-R can

be used in large-scale epidemiological studies, requires little or no judgment by an interviewer, and can be administered in a short period of time.[23] Thyroid function was investigated using third generation assays and a detailed interview about of use of medication. Limitations include the cross-sectional analysis, which does not permit any causal inference. Information about psychiatric disorders on follow-up will be available only in 2016, permitting future prospective analysis. TSH was measured only once; therefore, it is possible that nonthyroidal illness, which would have altered TSH levels, could have resulted in some kind of misclassification regarding thyroid function. FT4 was only measured in subjects with TSH <0·4 mIU/l and in subjects with TSH >4·0 mIU/l, but not for subjects with normal TSH values. We have no information about antithyroperoxidase antibodies. Therefore, we could not explore the relationship between thyroid autoimmunity and psychiatric disorders, as reported in previous studies.[45,46] Another limitation is that despite the large sample from ELSA-Brasil, some subgroup analyses were restricted to a small number of participants and results showed wide confidence intervals reflecting the small sample size. Hence, negative results should be interpreted with caution, as the analysis may simply be underpowered. More than that, as the frequency of psychiatric disorders[47] is high in areas of social inequalities in Brazil, it is possible that ELSA-Brasil sample is likely protected against these diseases because of the high-income and educational attainment of participants compared to the Brazilian population. Therefore, it is possible that our data give an underestimate compared to the general population in Brazil.

Conclusion

We found an association between subclinical hyperthyroidism and panic disorder and a possible protective effect of subclinical hypothyroidism for anxiety disorders. However, both lost significance after correction for multiple comparisons. The low number of subjects with panic disorders and the possible underestimation of psychiatric disorders in the sample compared to the Brazilian population could explain the results.

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References

1 Tunbridge, W.M., Evered, D.C., Hall, R. *et al.* (1977) The spectrum of thyroid disease in a community: the Wickham survey. *Clinical Endocrinology (Oxford)*, **7**, 481–493.

2 Vanderpump, M.P., Tunbridge, W.M., French, J.M. *et al.* (1995) The incidence of thyroid disorders in the community: a 20-year follow-up of the Wickham survey. *Clinical Endocrinology (Oxford)*, **43**, 55–68.

3 Dayan, C.M. & Panicker, V. (2013) Hypothyroidism and depression. *European Thyroid Journal*, **2**, 168–179.

4 Forman-Hoffman, V. & Philibert, R.A. (2006) Lower TSH and higher T4 levels are associated with current depressive syndrome in young adults. *Acta Psychiatrica Scandinavica*, **114**, 132–139.

5 Roberts, L.M., Pattison, H., Roalfe, A. *et al.* (2006) Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? *Annals of Internal Medicine*, **145**, 573–581.

6 De Jongh, R.T., Lips, P., van Schoor, N.M. *et al.* (2011) Endogenous subclinical thyroid disorders, physical and cognitive function, depression, and mortality in older individuals. *European Journal of Endocrinology*, **165**, 545–554.

7 Engum, A., Bjøro, T., Mykletun, A., Dahl, AA. *et al.* (2002) An association between depression, anxiety and thyroid function – a clinical fact or artifact? *Acta Psychiatrica Scandinavica*, **106**, 27–34.

8 Grabe, H.J., Völzke, H., Lüdermann, J. *et al.* (2005) Mental and physical complaints in thyroid disorders in the general population. *Acta Psychiatrica Scandinavica*, **112**, 286–293.

9 Panicker, V., Evans, J., Bjoro, T. *et al.* (2009) A paradoxical difference in relationship between anxiety, depression and thyroid function in subjects on and not on T4: findings from the HUNT study. *Clinical Endocrinology (Oxford)*, **71**, 574–580.

10 Larisch, R., Kley, K., Nikolaus, S. *et al.* (2004) Depression and anxiety in different thyroid function states. *Hormone and Metabolic Research*, **36**, 650–653.

11 Gulseren, S., Gulseren, H.Z., Cetinay, P. *et al.* (2006) Depression, anxiety, health-related quality of life, and disability in patients with overt and subclinical thyroid dysfunction. *Archives of Medical Research*, **37**, 133–139.

12 Kramer, C.K., von Mühlen, D., Kritz-Silverstein, D. *et al.* (2009) Treated hypothyroidism, cognitive function, and depressed mood in old age: the Rancho Bernardo Study. *European Journal of Endocrinology*, **161**, 917–921.

13 Williams, M.D., Harris, R., Dayan, C.M. *et al.* (2009) Thyroid function and the natural history of depression: findings from the Caerphilly Prospective Study (CaPS) and a meta-analysis. *Clinical Endocrinology (Oxford)*, **70**, 484–492.

14 Park, Y.J., Lee, E.J., Lee, Y.J. *et al.* (2010) Subclinical hypothyroidism (SCH) is not associated with metabolic derangement, cognitive impairment, depression or poor quality of life in elderly subjects. *Archives of Gerontology and Geriatrics*, **50**, e68–e73.

15 Benseñor, I.M., Goulart, A.C., Lotufo, P.A. *et al.* (2011) Prevalence of thyroid disorders among older people: results from the São Paulo Ageing & Health Study. *Cadernos de Saúde Pública*, **27**, 155–161.

16 Sichieri, R., Baima, J., Marante, T., *et al.* (2007) Low prevalence of hypothyroidism among black and Mulatto people in a population-based study of Brazilian women. *Clinical Endocrinology (Oxford)*, **66**, 803–807 Epub 2007 Mar 23.

17 Andrade, L.H., Wang, Y.K., Andreoni, S. *et al.* (2012) Mental disorders in megacities: findings from the São Paulo megacity mental health survey, Brazil. *PLoS ONE*, **7**, e31879.

18 Viana, M.C. & Andrade, L.H. (2012) Lifetime Prevalence, age and gender distribution and age-of-onset of psychiatric disorders

in the São Paulo Metropolitan Area, Brazil: results from the São Paulo Megacity Mental Health Survey. *Revista Brasileira de Psiquiatria*, **34**, 249–260.
19 Aquino, E.M., Barreto, S.M., Bensenor, I.M. *et al.* (2012) Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. *American Journal of Epidemiology*, **175**, 315–324.
20 Lotufo, P.A. (2013) Setting up the longitudinal study for adult health (ELSA-Brasil). *Revista de Saúde Pública*, **47**(Suppl 2), 3–9.
21 Schmidt, M.I., Duncan, B.B., Mill, J.G. *et al.* (2014) Cohort Profile: longitudinal Study of Adult Health (ELSA-Brasil). *International Journal of Epidemiology*, doi: 10.1093/ije/dyu027. [Epub ahead of print]
22 Bensenor, I.M., Griep, R.H., Pinto, K.A. *et al.* (2013) Routines of organization of clinical tests and interviews in the ELSA-Brasil investigation center. *Revista de Saúde Pública*, **47**(Suppl 2), 37–47.
23 Lewis, G., Pelosi, A.J., Araya, R. *et al.* (1992) Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychological Medicine*, **22**, 465–486.
24 WHO. (2010) International Statistical Classification of Diseases and Related Health Problems. 10th Revision.
25 Nunes, M.A., Alves, M., Chor, D. *et al.* (2011) Adaptação transcultural do CIS-R (Clinical Interview Schedule – Revised Version) para o português no estudo longitudinal de saúde do adulto (ELSA). *Revista do Hospital das Clínicas de Porto Alegre e a Faculdade de Medicina da Universidade Federal do Rio Grande do Sul*, **31**, 515–518.
26 Herdman, M., Fox-Rushby, J. & Badia, X. (1998) A model of equivalence in the cultural adaptation of HRQoL Instruments: the universalist approach. *Quality of life Research*, **7**, 323–335.
27 Hollowell, J.G., Staehling, N.W., Flanders, W.D. *et al.* (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988-1994): National Health and Nutritional Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism*, **87**, 489–499.
28 Surks, M.I., Ortiz, E., Daniels, G.H. *et al.* (2004) Subclinic thyroid disease – Scientific review and guidelines for diagnosis and management. *Journal of the American Medical Association*, **291**, 228–238.
29 Lai, E.C., Yang, Y.H., Lin, S.J. *et al.* (2013) Use of antiepileptic drugs and risk of hypothyroidism. *Pharmacoepidemiology and Drug Safety*, **22**, 1071–1079.
30 Dong, B.C. (2000) How medications affect thyroid function. *Western Journal of Medicine*, **172**, 102–106.
31 Roy-Byrne, P.P., Uhde, T.W., Rubinow, D.R. *et al.* (1986) Reduced TSH and prolactin responses to TRH in patients with panic disorder. *American Journal of Psychiatry*, **143**, 503–507.
32 Tukel, R., Kora, K., Hekim, N. *et al.* (1999) Thyrotropin stimulating hormone response to thyrotropin releasing hormone response in patients with panic disorder. *Psychoneuroendocrinology*, **24**, 155–160.
33 Yeragani, V.K., Rainey, J.M., Pohl, R. *et al.* (1987) Thyroid hormone levels in panic disorder. *Canadian Journal of Psychiatry*, **32**, 467–469.
34 Kikuchi, M., Komuro, R., Oka, H. *et al.* (2005) Relationship between anxiety and thyroid function in patients with panic disorder. *Progress in Neuro-Psychopharmacol and Biological Psychiatry*, **29**, 77–81.
35 Fardella, C., Gloger, S., Figueroa, R. *et al.* (2000) High prevalence of thyroid abnormalities in a Chilean psychiatric outpatients population. *Journal of Endocrinological Investigation*, **23**, 102–106.
36 Bensenor, I.M., Lotufo, P.A., Menezes, P.R. *et al.* (2010) Subclinical hyperthyroidism and dementia: the São Paulo Ageing & Health Study. *BioMed Central Public Health*, **10**, 298.
37 Guimarães, J.M., de Souza Lopes, C., Baima, J. *et al.* (2009) Depression symptoms and hypothyroidism in a population-based study of middle-aged Brazilian women. *Journal of Affective Disorders*, **117**, 120–123.
38 Chueiri, V.B., Romaldini, J.H. & Ward, L.S. (2006) Subclinical hypothyroidism increases the risk of depression in the elderly. *Archives of Gerontology and Geriatrics*, **44**, 21–28.
39 Teixeira, P.F., Reuters, V.S., Almeida, C.P. *et al.* (2006) Evaluation of clinical and psychiatric symptoms in subclinical hypothyroidism. *Revista da Associação Médica Brasileira*, **52**, 222–228.
40 Almeida, C., Brasil, M.A., Costa, A.J. *et al.* (2007) Subclinical hypothyroidism: psychiatric disorders and symptoms. *Revista Brasileira de Psiquiatria*, **29**, 157–159.
41 Vigário, P., Teixeira, P., Reuters, V. *et al.* (2009) Perceived health status of women with overt and subclinical hypothyroidism. *Medical Principles and Practice*, **18**, 317–322.
42 Hamilton, S.P., Fyer, A.J., Durner, M. *et al.* (2003) Further genetic evidence for a panic disorder syndrome mapping to chromosome 13q. *Proceeding of the National Academy of Sciences United Stated of America*, **100**, 2559–2555.
43 Belin, R.M., Astor, B.C., Power, N.F. *et al.* (2004) Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a high prevalence of mild thyrotropin concentration suppression in the Third National Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism*, **89**, 6077–6086.
44 Carlé, A., Pedersen, I.B., Knudsen, N. *et al.* (2012) Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case-control study. *European Journal of Endocrinology*, **167**, 483–490.
45 van de Ven, A.C., Muntjewerff, J.-W., Netea-Maier, R.T. *et al.* (2012) Association between thyroid function, thyroid autoimmunity, and state and trait factors of depression. *Acta Psychiatrica Scandinavica*, **126**, 377–384.
46 Engum, A., Bjoro, T., Mykletun, A. *et al.* (2005) Thyroid autoimmunity, depression and anxiety: are there any connections? An epidemiological study of a large population. *Journal of Psychosomatic Research*, **59**, 263–268.
47 Chiavegatto Filho, A.D., Kawachi, I., Wang, Y.P. *et al.* (2013) Does income inequality get under the skin? A multilevel analysis of depression, anxiety and mental disorders in Sao Paulo, Brazil. *Journal of Epidemiology and Community Health*, **67**, 966–972.