Reviewer's report

**Title:** Subclinical Hyperthyroidism and Dementia: the Sao Paulo Ageing & Health Study (SPAH), a cross-sectional study.

**Version:** 1  **Date:** 16 February 2010

**Reviewer:** Frank Jan J de Jong

The authors studied the cross-sectional relationship between thyroid function, especially subclinical hyperthyroidism, and dementia in a population-based cohort of low-income elderly. They found subclinical hyperthyroidism to increase the risk of dementia and Alzheimer’s disease, in particular in men. To my knowledge, this is the first report of a study addressing thyroid function in community-dwelling elderly in a lower income country.

The report is well written, the data collection sound. However, I would like to address a few major issues concerning the study hypothesis, data analysis, and the discussion and conclusions of the work.

First, the authors describe in their introduction that to date population-based studies found no consistent association of thyroid function with cognition or dementia in the elderly. This pertains to subclinical thyroid dysfunction, both subclinical hypo- and hyperthyroidism, and also thyroid function within the normal range. Yet, the authors choose to only address the aforementioned association between subclinical hyperthyroidism and dementia. Based on the literature there is no evidence for such an a priori restriction. It would be interesting to see whether there is also a relationship with subclinical hypothyroidism, and a linear or curvilinear association, if any, of thyroid function (both TSH and fT4) within the normal range, in particular given the large study sample. Over 1000 study participants with thyroid function in the normal range are now only used as a reference. If there is no obvious non-linear association, the authors could describe the association of TSH and fT4 per SD increase and prevalence of dementia. Else, TSH and fT4 could be divided in quintiles and the middle group could be used as a reference. In addition, TPO-Abs are also assessed and not studied in relation to dementia. Is their an association of elevated TPO-Abs and dementia? And if so, is it related to higher or lower thyroid function?

Second, the prevalence of both subclinical hyper- and hypothyroidism as well as dementia is quite low. It is therefore possible that the association is for a large part driven by a few men with Alzheimer’s disease. As a result, confidence intervals are very large, and the result is more likely to reflect a chance finding. This is an important issue and should be mentioned in the discussion.

Third, the authors present crude analyses and analyses after adjustment for age. Is age adjusted for as a continuous measure, or in quartiles? Adjusting per year
age increase is most appropriate. Other potential confounders, especially BMI, are not taken into account. Given that changes in thyroid function may reflect comorbidity, which is common in dementia, this is an important issue.

Although this is a cross-sectional study and the issue of causality cannot be addressed, the authors could elaborate on this issue in the discussion. Do they believe the hitherto reported associations of thyroid function with dementia are causal or do they reflect comorbidity?

According to my opinion the manuscript adheres to the relevant standards for reporting and data deposition. Limitations of the work are in part clearly stated and the authors clearly acknowledge any work upon which they are building. In addition, the title and abstract accurately convey what has been found. Finally, the writing is appropriate.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests