

RESEARCH

Spectrum of thyroid dysfunction and dementia: a dose–response meta-analysis of 344,248 individuals from cohort studies

Xingyao Tang^{1,*}, Zhi-Hui Song^{2,*}, Dawei Wang³, Jinkui Yang⁴, Marly Augusto Cardoso⁵, Jian-Bo Zhou^{1b} and Rafael Simó^{6,7}

¹Beijing Tongren Hospital, Capital Medical University, Beijing, China

²Department of Pharmacy, Beijing Tongren Hospital, Capital Medical University, Beijing, China

³General Practice Department, Beijing Tongren Hospital, Capital Medical University, Beijing, China

⁴Department of Endocrinology, Beijing Tongren Hospital, Capital Medical University, Beijing, China

⁵Department of Nutrition, School of Public Health, University of Sao Paulo, Sao Paulo, Brazil

⁶Endocrinology and Nutrition Department, Hospital Universitari Vall d'Hebron, Diabetes and Metabolism Research Unit, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

⁷Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

Correspondence should be addressed to J-B Zhou: jbzhou@ccmu.edu.cn

*(X Tang and Z-H Song contributed equally to this work)

Abstract

Thyroid hormone, as a modifiable risk factor for dementia, promotes neurocognitive function and regulates metabolic processes. Various studies have defined different thyroid-stimulating hormone cutoffs, but the safest thyroid-stimulating hormone concentration was absent. A dose–response meta-analysis describing the overall functional relation and identifying exposure intervals associated with a higher or lower disease risk is thus desirable. Therefore, our current analysis was conducted to understand the influence of thyroid dysfunction on dementia risk. We searched PubMed, Embase, and Web of Science before May 1, 2020 for human studies published in English. Studies were considered for inclusion if they used a cohort study design to measure the risk of dementia in different thyroid function status groups, diagnosed thyroid functional status and all-cause dementia, included participants aged >18 years, and provided quantitative measures of data. The analysis contained 17 articles with 344,248 individuals with a 7.8-year mean follow-up. Ten studies with 329,287 participants indicated that only subclinical hyperthyroidism was associated with an increased risk of dementia. In contrast, subclinical hypothyroidism, clinical hyperthyroidism, and clinical hypothyroidism did not affect dementia. In the dose–response meta-analysis with 46,417 samples from 11 studies, the association of thyroid-stimulating hormone with the risk of dementia exhibited a U-shaped curve. Our study indicated that subclinical hyperthyroidism was associated with the risk of dementia and the thyroid-stimulating hormone concentration at around 1.55–1.60 mU/L as the optimum range for the risk of dementia.

Key Words

- thyroid dysfunction
- dementia
- dose–response
- meta-analysis

Endocrine Connections
(2021) **10**, 410–421

Introduction

Dementia is a progressive disease with declining cognitive function and affects daily activities (1). The global prevalence of dementia is 1.2–7.2%, and the number of dementia patients is estimated to increase to 131.5 million by 2050 (2). Prevention of dementia is crucial owing to the lack of disease-modifying medication. Recent reports have declared that risk factor modifications could prevent 30–35% of dementia cases (3).

The thyroid hormone, as a modifiable risk factor for dementia, promotes neurocognitive function and regulation metabolic processes (4). Thyroid dysfunction, including clinical hyperthyroidism, subclinical hyperthyroidism, subclinical hypothyroidism, and clinical hypothyroidism, has been associated with an increased risk of cognitive impairment in many studies (5). A recent meta-analysis indicated a positive association between subclinical hyperthyroidism and an increased risk of dementia among prospective cohorts, while no such relationship existed in subclinical hypothyroidism (5). New evidence has emerged recently (6, 7, 8, 9), involving the impact of clinical hyperthyroidism and clinical hypothyroidism on the risk of dementia in a large sample size (7, 8).

For the diagnosis of thyroid dysfunction, the thyroid-stimulating hormone (TSH) (also known as thyrotropin) concentration was also measured as a risk factor for dementia (10, 11, 12, 13). Another meta-analysis combined 11 studies and found that TSH concentrations below the normal range had an increased risk of dementia (14). However, other studies have defined different TSH cutoffs. Moreover, a lower, but average serum TSH concentration, also pertained to negative impacts on the development and progression of cognitive function (15). Thus, a detailed analysis of the impact of specific TSH concentrations on dementia is desirable. A dose–response meta-analysis – aimed at describing the overall functional relation and identifying exposure intervals associated with a higher or lower disease risk – is also desirable.

Various studies have defined different thyroid-stimulating hormone cutoffs, but the safest thyroid-stimulating hormone concentration was absent. It is desirable to confirm the relationship between thyroid dysfunction and risk of dementia in prospective cohort studies as well as to conduct a dose–response meta-analysis using published findings to understand the influence of TSH concentration change, even within the normal range, on the risk of dementia.

Method

Study inclusion

For our analysis, we searched the PubMed and Embase databases and Web of Science for relevant studies published until May 1, 2020. All types of abnormal thyroid function and dementia were searched, including clinical hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, clinical hyperthyroidism, abnormal thyrotropin (TSH), dementia, Alzheimer's disease, and vascular dementia. Reference lists of eligible articles were searched for further pertinent articles. The screening was completed independently by two reviewers (X Y T, J B Z), and discrepancies, if any, were resolved with a discussion. This report was conducted according to the Meta-analysis of Observational Studies in Epidemiology (16) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (17).

Subclinical hypothyroidism was defined as high TSH concentrations but normal blood concentrations of thyroid hormones. Subclinical hyperthyroidism was defined as low TSH concentrations but normal blood concentrations of thyroid hormones. Clinical hypothyroidism was defined as high TSH concentrations and low blood concentrations of thyroid hormones. Clinical hyperthyroidism was defined as low TSH concentrations and high blood concentrations of thyroid hormones.

Inclusion and exclusion criteria

Studies were considered for inclusion if they (1) were an original article published in English, (2) used a cohort study design to measure the risk of dementia in different thyroid function status groups, (3) included participants aged > 18 years, and (4) provided quantitative measures of data. Exclusion criteria followed were (1) the publication was a review, case report, animal study, or letter to the editor, (2) the reviews did not clearly define clinical outcomes, (3) the authors could not provide valid data after being contacted, and (4) duplicated data.

For the meta-analysis, studies were included if they measured the risk of dementia between euthyroid and clinical hypothyroidism or subclinical hypothyroidism or subclinical hyperthyroidism or clinical hyperthyroidism. In the dose–response meta-analysis, studies with at least three categories of TSH concentrations and the number of dementia cases presented, according to the different categories of TSH concentrations, were retained.

Data extraction and quality assessment

Two investigators (X Y T, M A C) independently extracted the following data from the 17 enrolled studies using the same standardized protocol: concerning study design, population characteristics, follow-up years, TSH cutoff concentrations as well as outcomes. Two investigators (J B Z, M A C) independently utilized the Newcastle–Ottawa Quality Assessment Scale criteria (NOS) (18) to assess the risk of bias for the enrolled studies. We rated the quality of the studies by awarding stars in each domain following the guidelines of NOS. Discrepancies, if any, were resolved with a discussion between the investigators and other authors.

Statistical analysis

We used STATA (version 12.0, Stata Corporation, College Station, TX, USA) to conduct the current analysis.

Heterogeneity between studies was evaluated using the I^2 metric and the variance between studies using Tau^2 . Random-effects models were performed if $I^2 > 50\%$ to determine the association between different thyroid function status and the risk of dementia. Random-effects models provide more weight to smaller studies. They typically have wider CIs because the total effect is the average value of the real effect of each study, which not only focuses on the study of a large sample but also pays attention to all included studies to balance the effect of each study. Fixed-effects models were performed if $I^2 \leq 50\%$.

Risk ratios (RR) as a measure of association across all studies were pooled. If studies used a hazard ratio (HR), we regarded it as RR. RRs with a 95% CI were used to assess time-to-event outcomes in the cohort studies, from the data obtained directly from the articles. If studies had both unadjusted and covariate-adjusted odds ratios, we chose the one that adjusted for the maximum number of covariates. We calculated RRs and 95% CIs using data from some studies that provided only the number of dementia cases in both abnormal thyroid status and control groups. We performed a sensitivity analysis to examine the robustness of our findings by excluding one study at a time and recalculating the pooled estimates. Further sub-group analysis was conducted owing to the different types of thyroid dysfunction, including subclinical hyperthyroidism, subclinical hypothyroidism, clinical hypothyroidism, and clinical hyperthyroidism. Further analysis was performed only for those who had a diagnosis of Alzheimer's disease, a sub-type of dementia.

Sensitivity analysis was used to identify more potential resource of heterogeneity.

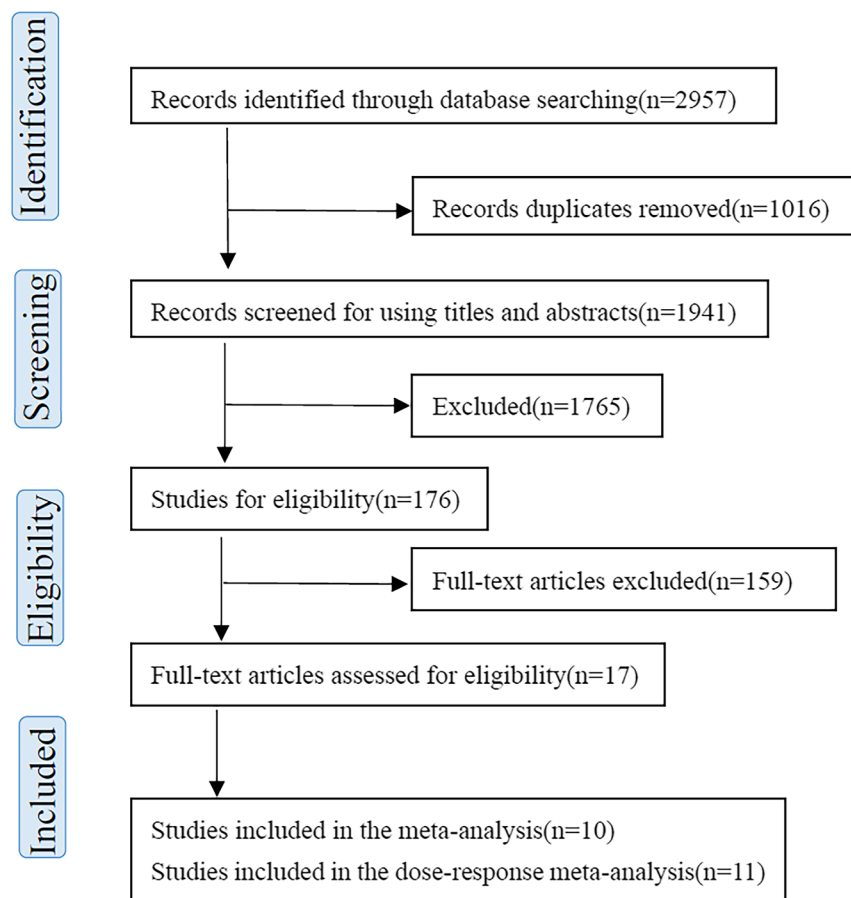
In the dose–response meta-analysis, we changed the reference group to the lowest dose group. The median concentration of TSH was chosen as the TSH category, and the number of dementia cases and the total participants were extracted. For the studies that did not present the median or mean doses of TSH, the midpoint of each category was chosen. The value for the open-ended upper interval was arbitrarily assigned as 1.5 times that of the lower end of the interval. The aggregate generalized least squares for trend (glst) method by Greenland and Longnecker was used for assessing the dose–response relationship between TSH and the risk of dementia (19). We used restricted cubic splines with three knots to explore a potential non-linear association between TSH concentrations and the risk of dementia.

Potential publication bias was evaluated using Egger's asymmetry test and with a visual inspection of a funnel plot (20). *P*-values were two-tailed, and $P < 0.05$ was considered significant.

Results

Literature search outcomes and validity assessment

The search strategy identified 2957 potentially relevant records, of which 1016 were excluded as duplicates. The remaining 1941 manuscripts were subjected to title and abstract screening. Further, 1765 publications were excluded, as they were reviews, letters or conference abstracts, and independent studies. Therefore, 176 articles were eligible for full-text review and data assessment. Finally, 159 articles were excluded owing to inadequate information or lack of a complete publication. A total of 17 cohort studies (6, 7, 8, 9, 10, 11, 12, 13, 15, 21, 22, 23, 24, 25, 26, 27, 28) published from 2000 to 2020 met the inclusion criteria (Fig. 1). Table 1 provides an overview of the eligible studies. All 17 studies used a longitudinal cohort design. The total number of participants was 344,248, with a mean follow-up duration of 7.8 years (2.1–21.9 years). The mean age of the participants was 65.1 years, and 50.1% were women. Ten studies (6, 7, 8, 10, 13, 21, 24, 25, 27, 28) were enrolled in the meta-analysis and eleven studies (6, 7, 10, 11, 13, 21, 24, 25, 26, 27, 28) were enrolled in the dose–response meta-analysis. Nine of them are present in both the analyses (6, 7, 10, 13, 21, 24, 25, 27, 28). Five other studies (9, 12, 15, 22, 23)


Figure 1

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study.

were not included in the meta-analysis or dose-response meta-analysis owing to irrelevant data.

Quality assessment

Quality assessment of the studies revealed scores of 5–9 on NOS. One study (28) was scored 5, another (9) was scored 6, four (10, 22, 23, 27) were scored 7, four (13, 15, 21, 24) were scored 8, and seven (6, 7, 8, 11, 12, 25, 26) were scored 9. High-quality studies were included (Table 1).

Meta-analysis of the association between abnormal thyroid function status and the risk of dementia

Ten studies (6, 7, 8, 10, 13, 21, 24, 25, 27, 28) with a sample size of 329,187 individuals provided effective data and were included in the current meta-analysis ($I^2 = 66.1\%$, $P = 0.000$). Four different abnormal thyroid function statuses were assessed: clinical hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, and clinical hyperthyroidism. Nine studies (6, 7, 8, 13, 21, 24, 25, 27, 28) mentioned subclinical hyperthyroidism,

eight (6, 7, 10, 13, 21, 24, 27, 28) mentioned subclinical hypothyroidism, while two (7, 8) mentioned clinical hyperthyroidism, and one (7) mentioned clinical hypothyroidism. Supplementary Table 2 (see section on [supplementary materials](#) given at the end of this article) provides the meta-analysis data.

The pooled effect value of the relationship between thyroid status and the risk of dementia was not significant ($RR = 1.14$, 95% CI: 0.97–1.35). Further sub-group analysis exhibited that subclinical hyperthyroidism increased the risk of dementia ($RR = 1.39$, 95% CI: 1.08–1.79), while subclinical hypothyroidism, clinical hyperthyroidism, and clinical hypothyroidism had no effect ($RR = 0.96$, 95% CI: 0.75–1.22, $RR = 1.06$, 95% CI: 0.63–1.79 and $RR = 0.96$, 95% CI: 0.73–1.26, respectively) (Fig. 2).

Three studies (10, 13, 24), with 3410 individuals, further mentioned subclinical thyroid dysfunction affecting the risk of Alzheimer's disease. The results showed no association between subclinical thyroid dysfunction, including subclinical hyperthyroidism ($RR = 1.52$, 95% CI: 0.69–3.32) and subclinical hypothyroidism ($RR = 1.15$, 0.68–1.94), and the risk of Alzheimer's disease ($RR = 1.25$, 95% CI: 0.81–1.94) (Fig. 1).

Table 1 Characteristics of studies included.

Study	Year	Country	Sample size	Women, %	Mean age (s.d.)	Follow-up (years)	Abnormal thyroid status definition	TSH cutoff level (mU/L)	Results	NOS
Kalmijn	2000	Netherlands	1843	61.90	68.8 (7.5)	2.1	Subclinical hypothyroidism: TSH > 4 mU/L, FT4 11–25 pmol/L; subclinical hyperthyroidism: TSH < 0.4 mU/L, FT4 11–25 pmol/L	0.4–4.0	Subclinical hyperthyroidism in the elderly increases the risk of dementia and Alzheimer's disease.	8
Annerbo	2006	Sweden	93	51.60	64.7 (9.2)	6	/	0.2–4.0	Lower TSH levels were found to be predictive factors of Alzheimer's disease.	7
de Jong	2006	Netherlands	1077	51.20	72.3 (7.4)	5.5	Subclinical hypothyroidism: TSH > 4.3 mU/L, FT4 0.85–1.94 ng/dL, T3 92.8–162.9 ng/dL; subclinical hyperthyroidism: TSH < 0.4 mU/L, FT4 0.85–1.94 ng/dL, T3 92.8–162.9 ng/dL	0.4–4.3	TSH and thyroid hormones were not associated with the risk of dementia or Alzheimer's disease.	8
Tan	2008	USA	1864	59.00	71 (7)	12.7	/	0.5–5.0	Low and high thyrotropin levels were associated with an increased risk of incident Alzheimer's disease in women but not in men.	9
Annerbo	2009	Sweden	200	79.50	81.0 (4.6)	6.7	/	0.2–4.0	TSH is not involved in the development of Alzheimer's disease.	7
de Jong	2009	Hawaii	665	0	78.1 (5.7)	4.7	Subclinical hypothyroidism: TSH > 4.3 mU/L, FT4 0.85–1.94 ng/dL; subclinical hyperthyroidism: TSH < 0.4 mU/L, FT4 0.85–1.94 ng/dL	0.4–4.3	No associations were found for TSH and dementia or Alzheimer's disease.	7
Vadivelu	2011	UK	12115	77.40	66.2 (16.4)	5.6	Subclinical hyperthyroidism: TSH ≤ 0.4 mU/L, FT4 10–25 pmol/L or total T4 65–155 nmol/L and total T3 0.9–2.6 nmol/L	0.4–4.0	Subclinical hyperthyroidism patients were associated with an increased risk of dementia.	9
Forti	2012	Italy	660	52.90	73.3 (6.0)	3.8	Subclinical hypothyroidism: TSH > 4.50 mU/L, FT4 10.3–25.7 pmol/L	0.45–4.5	Baseline TSH was not related to the risk of developing Alzheimer's disease, but high TSH was associated with an increased risk of vascular dementia.	7

(Continued)

Table 1 Continued.

Study	Year	Country	Sample size	Women, %	Mean age (s.d.)	Follow-up (years)	Abnormal thyroid status definition	TSH cutoff level (mU/L)	Results	NOS
Yeap	2012	Australia	3401	0	76.8 (3.5)	5.9	Subclinical hypothyroidism: TSH > 4.0 mU/L, FT4 ≥ 10 pmol/L	0.4–4.0	There was no association between TSH quartiles and incident dementia.	8
Formiga	2014	Spain	307	54.60	85.0 (0.0)	3	Subclinical hypothyroidism: TSH > 5.0 mU/L, FT4 0.85–1.94 ng/dL; subclinical hyperthyroidism: TSH < 0.25 mU/L, FT4 0.85–1.94 ng/dL	0.25–5.0	Subclinical hypo- and hyperthyroidism were not associated with an increased risk of dementia.	5
Moon	2014	Korea	313	50	72.5 (6.9)	5	/	0.4–4.1	Lower serum TSH level within the reference range was independently associated with the risk of dementia in elderly subjects.	8
Cappola	2015	USA	2843	56.20	74.5 (5.1)	17	/	0.45–4.5	Individuals with TSH in the fourth quartile had a 9.6 per 1000 person-year lower incidence of dementia.	9
Chaker	2016	Netherlands	9446	56.70	64.9 (9.7)	8	/	0.4–4.0	High and high-normal thyroid function is associated with increased dementia risk.	9
Aubert	2017	USA	2558	51.80	75.1 (2.8)	9	Subclinical hypothyroidism: TSH > 4.50 mU/L, FT4 10.3–23.2 pmol/L; subclinical hyperthyroidism: TSH < 0.45 mU/L, FT4 10.3–23.2 pmol/L	0.45–4.49	Among older adults, subclinical hyperthyroidism with a TSH < 0.10 mU/L was associated with a higher risk of dementia.	9
George	2019	USA	12481	56	57 (5.7)	21.9	Clinical hypothyroidism: TSH > 5.1 mU/L, FT4 < 0.85 ng/dL; subclinical hypothyroidism: TSH > 5.1 mU/L, FT4 0.85–1.4 ng/dL; subclinical hyperthyroidism: TSH < 0.56 mU/L, FT4 0.85–1.4 ng/dL; clinical hyperthyroidism: TSH < 0.56 mU/L, FT4 > 1.4 ng/dL	0.56–5.1	Subclinical hypothyroidism was associated with a reduced risk of dementia, whereas overt hyperthyroidism, particularly very elevated FT4, was associated with an increased risk of dementia.	9

Quinlan	2019	Sweden	302	54	65.0 (7.8)	2.8	/	0.3–4.2	6
Folkestad	2020	Denmark	Danish National Patient registry (DNPR) cohort: 280640 OPENTHYRO register cohort: 13440	/	DNPR cohort: 65 (54–75) OPENTHYRO register cohort: 62 (49–74)	7.2 7.3	Subclinical hyperthyroidism: TSH < 0.3 mU/L, T4 < 135.0 nmol/L, T3 < 2.2 nmol/L; clinical hyperthyroidism: TSH < 0.3 mU/L, T4 > 135.0 nmol/L and/or T3 > 2.2 nmol/L	0.3–4.0	9
TSH did not associate with dementia. Every 6 months of decreased TSH was associated with an increased risk of dementia by 16%, compared to individuals with normal TSH.									

FT3, free triiodothyronine; FT4, free thyroxine; NOS, score of Newcastle–Ottawa Scale; TSH, thyroid-stimulating hormone.

Sensitivity analysis

Sensitivity analyses demonstrated similar results, indicating that the overall results were not significantly influenced by any single study, with RRs and 95% CIs ranging from 1.11 (0.94–1.31) to 1.23 (0.99–1.52) for the risk of dementia.

We limited the analysis to individuals aged >65 years (6, 10, 13, 21, 24, 25, 27, 28) and found similar results. Subclinical hyperthyroidism was significantly linked to the risk of dementia (RR=1.51, 95% CI: 1.21–1.89), while subclinical hypothyroidism did not affect dementia (RR=1.03, 95% CI: 0.84–1.25). Furthermore, we limited the analysis to studies with NOS scores ≥ 7 (6, 7, 8, 10, 13, 21, 24, 25, 27). Subclinical hyperthyroidism increased the risk of dementia (RR=1.40, 95% CI: 1.08–1.83), while subclinical hypothyroidism was not a risk factor for dementia (RR=0.91, 95% CI: 0.71–1.44). The effect of clinical thyroid dysfunction on dementia remains unchanged.

Dose-response meta-analysis of the association between TSH concentrations and the risk of dementia

As most primary studies analyzed reported different cutoffs of TSH, we further performed a dose-response meta-analysis. A total of 11 studies (6, 7, 10, 11, 13, 21, 24, 25, 26, 27, 28) containing 46,417 individuals with more than three categories of TSH concentrations were analyzed. Supplementary Table 3 provides data of the dose-response meta-analysis.

A non-linear relationship was observed between the TSH concentrations and the risk of dementia. The graph showed that both low and high TSH concentrations had adverse effects, which indicated that not only hyperthyroidism but also hypothyroidism might lead to dementia. Using a restricted cubic spline model, we found that 1.55–1.60 mU/L was the safest concentration of TSH for preventing dementia. Lower or higher TSH concentrations increased the risk of dementia, even TSH concentrations were in the upper and lower limits of normal range. The most and second harmful TSH concentration for the risk of dementia was measured as lower than 0.05 (RR=1.46, 95% CI: 1.31–1.64) mU/L and higher than 5.39 mU/L (RR=1.44, 95% CI: 1.22–1.69), respectively. We added age and follow-up years as covariates, and the results showed no change (Fig. 3).

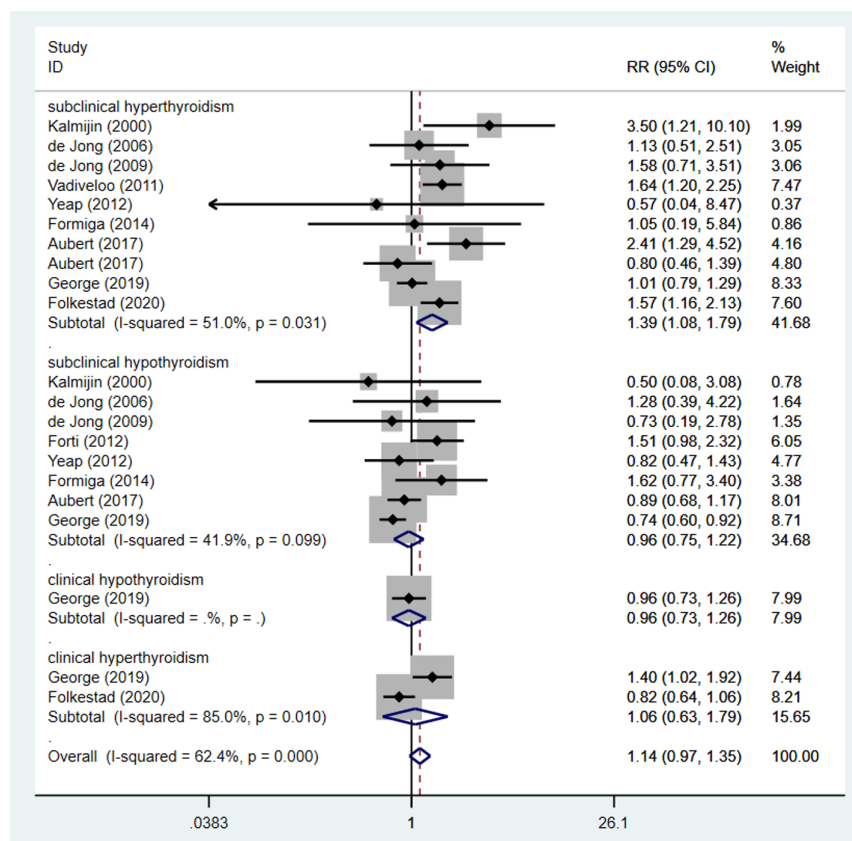


Figure 2

The association between thyroid dysfunction and dementia. RR, ratio risk. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random-effects estimate of sub-group analysis studies. Weights are from the random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the gray boxes around the point estimates reflect the weight assigned to each study.

Publication bias

According to the Cochrane Handbook version (29), as a rule of thumb, tests for funnel plot asymmetry should be used only when an adequate number of studies are included in the meta-analysis, as with very few studies, the power of the tests is extremely low to distinguish chance from real asymmetry. In this study, the P -value of Egger's test was > 0.05 ($P=0.225$), for the relationship between thyroid function and dementia, indicating no significant bias among them. The funnel figure of these studies showed asymmetrical inverted distribution, which is consistent with the results of Egger's test (Fig. 2).

Discussion

The current analysis comprised 17 cohort studies, including 4 different thyroid dysfunctions (clinical hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, and clinical hyperthyroidism) and different TSH concentration range. In the meta-analysis, 10 studies with 329,287 thirty participants indicated that only subclinical hyperthyroidism was associated with increased risk of dementia (RR = 1.39, 95% CI: 1.08–1.79).

In contrast, subclinical hypothyroidism, clinical hyperthyroidism, and clinical hypothyroidism did not affect the risk of dementia. Furthermore, the optimum concentration of TSH was 1.55–1.60 mU/L is. Both lower and higher concentrations of TSH were associated with the increased risk of dementia, even TSH concentrations were in the upper and lower limits of normal range.

Comparison with other studies

The current analysis contained entirely of cohort studies and demonstrated subclinical hyperthyroidism as the sole risk factor for dementia. Two cross-sectional studies with 2072 (30) and 119 (31) samples indicated a similar association between subclinical hyperthyroidism and dementia. Our findings were in line with a recent cross-sectional study, with 918 participants, which demonstrated that subclinical hypothyroidism did not affect dementia (32). Our results verified the findings of a meta-analysis conducted in 2016 after adding three new reports (6, 7, 8). Compared with the former meta-analysis, we further analyzed the relationship between clinical hypothyroidism and clinical hyperthyroidism with dementia and conducted a dose-response analysis aimed

at determining the effects of different TSH concentrations on the risk of dementia.

Although in our meta-analysis, clinical thyroid dysfunction had no effect on dementia, the evidence was limited and needed more reliable reports for confirmation. The difference between the effect of clinical and subclinical hyperthyroidism on dementia may be explained by the lack of treatment and extended duration of thyroid dysfunction in patients with subclinical hyperthyroidism (33). Individuals with subclinical hyperthyroidism are less likely to receive treatment than those with clinical hyperthyroidism, which may influence dementia. In the current meta-analysis, one study (7) showed the relationship between clinical hypothyroidism and clinical hyperthyroidism with dementia, and we chose the model that adjusted for the baseline thyroid medication use. Another study (8) contained the relationship between clinical hyperthyroidism and dementia, but the treatment methods were not mentioned. Thus, further analysis could not be carried out. As an important laboratory indicator of clinical hyperthyroidism, free thyroxine (FT4) is another important hormone related to dementia, and a former meta-analysis found that per standard deviation (s.d.) increment of FT4 was associated with the increased risk of dementia (RR=1.08, 95% CI: 1.00–1.17) (14). Owing to the limited evidence of the relationship between dementia and clinical hyperthyroidism, we did not include FT4 concentrations for further analysis.

Because of the different definitions of TSH cutoff concentrations, we performed a dose-response meta-analysis of the relationship between TSH concentrations and dementia. The results suggested the optimal cutoff of TSH to be 1.55–1.60 mU/L. Compared with 1.55–1.60 mU/L of TSH, both lower than 1.55 mU/L TSH and higher than 1.60 mU/L TSH increased the risk of dementia,

even within a normal range. A recent meta-analysis declared TSH concentrations below the normal range as a risk factor for dementia, while TSH concentrations within the normal range and above the normal range had no significant influence on dementia (14). Moreover, the linear model showed a significant association between the per s.d. increment of TSH and dementia (RR=0.91, 95% CI: 0.84–0.99). Some other studies paid attention to the influence of TSH on dementia only with respect to a linear relationship. One report (15) declared per unit decrease of TSH within the normal range (0.4–4.1 mU/L) increased the risk of dementia (HR=0.583, 95% CI: 0.403–0.843), while another (12) found no link of per TSH unit increase with dementia (HR=0.88, 95% CI: 0.76–1.01). Our analysis further clarified the effect of different TSH concentrations on dementia in the non-linear model and found a U-shaped relationship. The normal range of TSH is widely considered as 0.5–4.5 mU/L, and the dose range with the lowest risk of dementia was 1.55–1.60 mU/L in the current analysis, which is closer to the lower limit of the normal range. However, the different effects of subclinical hypothyroidism and higher TSH concentrations on dementia are unclear and need additional evidence to elucidate.

Potential mechanisms

Thyroid dysfunction and dementia may be linked through potential pathways. The thyroid hormone has been suggested to promote neuroprotection and regulate neurogenesis (34). However, long-term exposure of the thyroid hormone can lead to cardiovascular and cerebrovascular diseases such as fibrillation and systolic hypertension, which are both associated with the risk of dementia (35). An alternate explanation is to elucidate the relationship between the thyroid hormone and the amount and phosphorylation of tau protein (36). High concentrations of the thyroid hormone may increase reactive oxygen species and reduce antioxidant enzymes, which may cause cellular damage and make the brain more vulnerable to amyloid toxicity (37). Finally, as a result of genetic susceptibility, excess thyroid hormone may alter gene expression in relevant pathways, such as neurogenesis (34).

Public health impact

Dementia is a growing clinical and socio-economic problem of aging societies. Recent estimates suggested more than 47 million individuals worldwide are affected

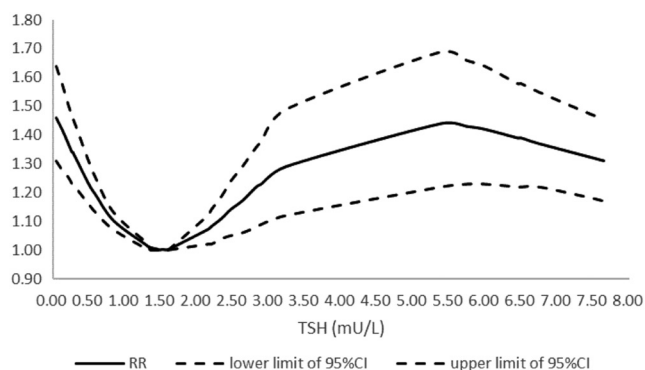


Figure 3

The dose-response association between TSH concentration and dementia. TSH, thyroid-stimulating hormone; RR, ratio risk.

by dementia (1). Thyroid dysfunction had an adverse impact on many aspects, including diabetes, elevated blood pressure, metabolic syndrome, heart failure, and cardiovascular disease (38). Regulation of thyroid function is beneficial to health. Our analyses demonstrated an increased risk of lower and higher TSH concentrations on dementia, even within a normal range. The optimum concentration of TSH was suggested as 1.55–1.60 mU/L. With the increasing prevalence of thyroid dysfunction, it may be valuable for public health to focus on monitoring TSH concentrations.

Strengths and limitations of the study

Our meta-analysis and dose–response meta-analysis produced valuable information regarding associations between thyroid dysfunction and TSH concentrations with the risk of dementia. Some desirable strengths and limitations must be outlined. The strengths of our analysis included choosing data that adjusted for the maximum number of covariates, developing a comprehensive search strategy, and conducting a comprehensive search.

There were also a few limitations. (1) Studies focused on the relationship of clinical hyperthyroidism and clinical hypothyroidism with the risk of dementia are few. Additional reliable evidence is needed to clarify the relationships. (2) In the current study, the lack of data on treatment and the effects of treatment on thyroid dysfunction limited a more rigorous analysis. Some reports declared the impacts of antithyroid drugs on dementia (39). The influence of antithyroid drugs on dementia needs additional research. (3) Some other factors may influence the concentration of TSH, such as pituitary-related disease (40). Further analysis was not performed owing to the limited information. (4) The heterogeneity of results may be due to differences in race, method of TSH measurement, and the definition of thyroid dysfunction. Owing to inadequate information, it was difficult to analyze the heterogeneity further.

Conclusion

Our study indicated that subclinical hyperthyroidism is associated with the risk of dementia, and the TSH concentration at around 1.55–1.60 mU/L was the peak range for the risk of dementia. Thus, it is desirable for public health to manage TSH concentrations, especially in those with a higher risk of dementia. However, validating and replicating these findings in more rigorously designed

studies is desirable. It may be valuable for further studies to pay more attention to the safest TSH and FT4 concentrations.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-21-0047>.

Declarations of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82070851, 81870556, 81930019, 81670738), Beijing Municipal Administration of Hospital's Youth Program (QML20170204), Excellent Talents in Dongcheng District of Beijing.

Acknowledgements

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

References

- Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, *et al.* Dementia prevention, intervention, and care. *Lancet* 2017 **390** 2673–2734. ([https://doi.org/10.1016/S0140-6736\(17\)31363-6](https://doi.org/10.1016/S0140-6736(17)31363-6))
- Vargas DM, De Bastiani MA, Zimmer ER & Klamt F. Alzheimer's disease master regulators analysis: search for potential molecular targets and drug repositioning candidates. *Alzheimers Research Therapy* 2018 **10** 59. (<https://doi.org/10.1186/s13195-018-0394-7>)
- Norton S, Matthews FE, Barnes DE, Yaffe K & Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet: Neurology* 2014 **13** 788–794. ([https://doi.org/10.1016/S1474-4422\(14\)70136-X](https://doi.org/10.1016/S1474-4422(14)70136-X))
- Cheng SY, Leonard JL & Davis PJ. Molecular aspects of thyroid hormone actions. *Endocrine Reviews* 2010 **31** 139–170. (<https://doi.org/10.1210/er.2009-0007>)
- Rieben C, Segna D, da Costa BR, Collet TH, Chaker L, Aubert CE, Baumgartner C, Almeida OP, Hogervorst E, Trompet S, *et al.* Subclinical thyroid dysfunction and the risk of cognitive decline: a meta-analysis of prospective cohort studies. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 4945–4954. (<https://doi.org/10.1210/jc.2016-2129>)
- Aubert CE, Bauer DC, da Costa BR, Feller M, Rieben C, Simonsick EM, Yaffe K, Rodondi N & Health ABC Study. The association between subclinical thyroid dysfunction and dementia: the Health, Aging and Body Composition (Health ABC) Study. *Clinical Endocrinology* 2017 **87** 617–626. (<https://doi.org/10.1111/cen.13458>)
- George KM, Lutsey PL, Selvin E, Palta P, Windham BG & Folsom AR. Association between thyroid dysfunction and incident dementia in the atherosclerosis risk in communities neurocognitive study. *Journal of Endocrinology and Metabolism* 2019 **9** 82–89. (<https://doi.org/10.14740/jem588>)
- Folkestad L, Brandt F, Lillevang-Johansen M, Brix TH & Hegedüs L. Graves' disease and toxic nodular goiter, aggravated by duration

- of hyperthyroidism, are associated with Alzheimer's and vascular dementia: a registry-based long-term follow-up of two large cohorts. *Thyroid* 2020 **30** 672–680. (<https://doi.org/10.1089/thy.2019.0672>)
- 9 Quinlan P, Horvath A, Wallin A & Svensson J. Low serum concentration of free triiodothyronine (FT3) is associated with increased risk of Alzheimer's disease. *Psychoneuroendocrinology* 2019 **99** 112–119. (<https://doi.org/10.1016/j.psychneu.2018.09.002>)
 - 10 Forti P, Olivelli V, Rietti E, Maltoni B, Pirazzoli G, Gatti R, Gioia MG & Ravaglia G. Serum thyroid-stimulating hormone as a predictor of cognitive impairment in an elderly cohort. *Gerontology* 2012 **58** 41–49. (<https://doi.org/10.1159/000324522>)
 - 11 Tan ZS, Beiser A, Vasan RS, Au R, Auerbach S, Kiel DP, Wolf PA & Seshadri S. Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Archives of Internal Medicine* 2008 **168** 1514–1520. (<https://doi.org/10.1001/archinte.168.14.1514>)
 - 12 Cappola AR, Arnold AM, Wolczyn K, Carlson M, Robbins J & Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 1088–1096. (<https://doi.org/10.1210/jc.2014-3586>)
 - 13 de Jong FJ, den Heijer T, Visser TJ, de Rijke YB, Drexhage HA, Hofman A & Breteler MM. Thyroid hormones, dementia, and atrophy of the medial temporal lobe. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 2569–2573. (<https://doi.org/10.1210/jc.2006-0449>)
 - 14 Wu Y, Pei Y, Wang F, Xu D & Cui W. Higher FT4 or TSH below the normal range are associated with increased risk of dementia: a meta-analysis of 11 studies. *Scientific Reports* 2016 **6** 31975. (<https://doi.org/10.1038/srep31975>)
 - 15 Moon JH, Park YJ, Kim TH, Han JW, Choi SH, Lim S, Park DJ, Kim KW & Jang HC. Lower-but-normal serum TSH level is associated with the development or progression of cognitive impairment in elderly: Korean Longitudinal Study on Health and Aging (KLoSHA). *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 424–432. (<https://doi.org/10.1210/jc.2013-3385>)
 - 16 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA & Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000 **283** 2008–2012. (<https://doi.org/10.1001/jama.283.15.2008>)
 - 17 Moher D, Liberati A, Tetzlaff J, Altman DG & PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009 **6** e1000097. (<https://doi.org/10.1371/journal.pmed.1000097>)
 - 18 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology* 2010 **25** 603–605. (<https://doi.org/10.1007/s10654-010-9491-z>)
 - 19 Greenland S & Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *American Journal of Epidemiology* 1992 **135** 1301–1309. (<https://doi.org/10.1093/oxfordjournals.aje.a116237>)
 - 20 Egger M, Davey Smith G, Schneider M & Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997 **315** 629–634. (<https://doi.org/10.1136/bmj.315.7109.629>)
 - 21 Yeap BB, Alfonso H, Chubb SA, Puri G, Hankey GJ, Flicker L & Almeida OP. Higher free thyroxine levels predict increased incidence of dementia in older men: the Health in Men Study. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E2230–E2237. (<https://doi.org/10.1210/jc.2012-2108>)
 - 22 Annerbo S, Kivipelto M & Lökk J. A prospective study on the development of Alzheimer's disease with regard to thyroid-stimulating hormone and homocysteine. *Dementia and Geriatric Cognitive Disorders* 2009 **28** 275–280. (<https://doi.org/10.1159/000242439>)
 - 23 Annerbo S, Wahlund LO & Lökk J. The significance of thyroid-stimulating hormone and homocysteine in the development of Alzheimer's disease in mild cognitive impairment: a 6-year follow-up study. *American Journal of Alzheimer's Disease and Other Dementias* 2006 **21** 182–188. (<https://doi.org/10.1177/1533317506289282>)
 - 24 Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA & Breteler MM. Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. *Clinical Endocrinology* 2000 **53** 733–737. (<https://doi.org/10.1046/j.1365-2265.2000.01146.x>)
 - 25 Vadiveloo T, Donnan PT, Cochrane L & Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1344–1351. (<https://doi.org/10.1210/jc.2010-2693>)
 - 26 Chaker L, Wolters FJ, Bos D, Korevaar TI, Hofman A, van der Lugt A, Koudstaal PJ, Franco OH, Dehghan A, Vernooij MW, *et al.* Thyroid function and the risk of dementia: the Rotterdam Study. *Neurology* 2016 **87** 1688–1695. (<https://doi.org/10.1212/WNL.0000000000003227>)
 - 27 de Jong FJ, Masaki K, Chen H, Remaley AT, Breteler MM, Petrovitch H, White LR & Launer LJ. Thyroid function, the risk of dementia and neuropathologic changes: the Honolulu-Asia aging study. *Neurobiology of Aging* 2009 **30** 600–606. (<https://doi.org/10.1016/j.neurobiolaging.2007.07.019>)
 - 28 Formiga F, Ferrer A, Padros G, Contra A, Corbella X, Pujol R & Octabaix Study Group. Thyroid status and functional and cognitive status at baseline and survival after 3 years of follow-up: the OCTABAIX study. *European Journal of Endocrinology* 2014 **170** 69–75. (<https://doi.org/10.1530/EJE-13-0722>)
 - 29 Higgins JPT, Thomas J, Chandler J, Cumpston M & Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions*.
 - 30 Benseñor IM, Lotufo PA, Menezes PR & Scazufca M. Subclinical hyperthyroidism and dementia: the Sao Paulo Ageing and Health Study (SPAH). *BMC Public Health* 2010 **10** 298. (<https://doi.org/10.1186/1471-2458-10-298>)
 - 31 Döbert N, Hamscho N, Menzel C, Peters J, Frölich L, Tsolakis A, Zaplatnikov K, Kratzsch T, Diener J, Maurer K, *et al.* Subclinical hyperthyroidism in dementia and correlation of the metabolic index in FDG-PET. *Acta Medica Austriaca* 2003 **30** 130–133.
 - 32 Park YJ, Lee EJ, Lee YJ, Choi SH, Park JH, Lee SB, Lim S, Lee WW, Jang HC, Cho BY, *et al.* Subclinical hypothyroidism (SCH) is not associated with metabolic derangement, cognitive impairment, depression or poor quality of life (QoL) in elderly subjects. *Archives of Gerontology and Geriatrics* 2010 **50** e68–e73. (<https://doi.org/10.1016/j.archger.2009.05.015>)
 - 33 Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH & Hegedüs L. Excess mortality in treated and untreated hyperthyroidism is related to cumulative periods of low serum TSH. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 2301–2309. (<https://doi.org/10.1210/jc.2017-00166>)
 - 34 Kapoor R, Fanibunda SE, Desouza LA, Guha SK & Vaidya VA. Perspectives on thyroid hormone action in adult neurogenesis. *Journal of Neurochemistry* 2015 **133** 599–616. (<https://doi.org/10.1111/jnc.13093>)
 - 35 Reddy V, Taha W, Kundumadam S & Khan M. Atrial fibrillation and hyperthyroidism: a literature review. *Indian Heart Journal* 2017 **69** 545–550. (<https://doi.org/10.1016/j.ihj.2017.07.004>)
 - 36 Oyanagi K, Negishi T & Tashiro T. Action of thyroxine on the survival and neurite maintenance of cerebellar granule neurons in culture. *Journal of Neuroscience Research* 2015 **93** 592–603. (<https://doi.org/10.1002/jnr.23519>)
 - 37 Aslan M, Cosar N, Celik H, Aksoy N, Dulger AC, Begenic H, Soyoral YU, Kucukoglu ME & Selek S. Evaluation of oxidative status in patients with hyperthyroidism. *Endocrine* 2011 **40** 285–289. (<https://doi.org/10.1007/s12020-011-9472-3>)

- 38 Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, Cappola TP & Cappola AR. Thyroid dysfunction in heart failure and cardiovascular outcomes. *Circulation: Heart Failure* 2018 **11** e005266. (<https://doi.org/10.1161/CIRCHEARTFAILURE.118.005266>)
- 39 Wändell P, Carlsson AC, Li X, Sundquist J & Sundquist K. Levothyroxine treatment and incident dementia in adults with atrial

- fibrillation. *Aging Clinical and Experimental Research* 2020 **32** 433–439. (<https://doi.org/10.1007/s40520-019-01217-3>)
- 40 Yamamoto M, Iguchi G, Bando H, Kanie K, Hidaka-Takeno R, Fukuoka H & Takahashi Y. Autoimmune pituitary disease: new concepts with clinical implications. *Endocrine Reviews* 2020 **41** bnz003. (<https://doi.org/10.1210/endrev/bnz003>)

Received in final form 1 March 2021

Accepted 19 March 2021

Accepted Manuscript published online 19 March 2021