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Association Between Hypothyroidism And Dementia: A Systematic Review

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ABSTRACT

Background: Dementia is a disabling syndrome of elderly population characterized by decline in memory, cognitive functions and behavioral changes, gravely reduces the quality of life. Thyroid hormones have vital importance for neural development and their dysfunction (deficiency or increase) can lead to changes in cognitive functions particularly memory decline.

Methods: A systematic review was conducted using studies retrieved from PubMed, EMBASE, Google scholar, Science Direct, and Cochrane library, as well as manual retrieval of studies from the bibliographies of selected studies. Original studies published in English in last 20 years (2004-2024) were included. The extracted data was represented on a common form to describe the study setting, population, authors name, year of study, demographic and baseline characteristics of each study.

Results: This systematic review examined total Nine studies. Six out of nine studies showed a very strong and significant association between hypothyroidism and dementia. Three remaining studies were failed to show any association in between these two entities. There was female predominance in most of the studies. Results showed that the risk of dementia in hypothyroid individuals increased with increasing age and duration of hypothyroidism.

Conclusion: There is a strong association found in between hypothyroidism and dementia (cognitive decline) in most of the studies but still there is a need of large scale prospective randomized studies in future to establish this association.

Key Words: Dementia, Thyroid abnormalities, Cognitive impairment.

Background:

Dementia is a disabling syndrome of elderly population characterized by decline in memory, cognitive functions and behavioral changes, gravely reduces the quality of life. Dementia is currently the 7th leading cause of death and one of the major causes of disability and dependency among older population globally (1). Recent reports have indicated that risk factors control could prevent 30-35% of dementia cases (2). It is estimated that approximately more than 57 million people in the world are currently living with dementia (3) and in the UK approximately 1 million people are living with dementia and this burden may increase up to 1.4 million in 2040 (4).

The thyroid gland produces T3 and T4 from dietary iodine. TSH is the hormone which promotes the release of FT3 and FT4 which are essential to stimulate cellular energy use and increase the metabolism. Thyroid hormones have vital importance for neural development and their dysfunction (deficiency or increase) can lead to changes in cognitive functions particularly memory decline (5). Samuels MH (6) in 2014 performed a double-blinded randomized crossover study on 19 subjects and observed significant decline in working memory at the end of subclinical hypothyroidism phase as compared with that measured at the end of euthyroid phase. Annerbo S & Lokk J (7) in 2013 found the association between subclinical hypothyroidism and cognitive impairment in community residents and hospitalized elderly. Kim JM & colleagues in his study have observed the significant association of clinical hypothyroidism, thyroiditis, and hyperthyroidism with Alzheimer's disease (8).

Considering the significance & economic burden of this disease we planned to conducted this systemic review to look for and describe the association between hypothyroidism and dementia/cognitive decline and to critically appraise the existing studies on this particular topic.

Methods:

This study was conducted in accordance with the Preferred Reporting items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. It is a systematic review including several studies done on the particular topic worldwide with no restriction of location. The studies which have higher participants

number and are specifically Case-control studies, Cohort or Randomized control trials were chosen for this comprehensive review. This method of research is selected to encompass a wider range of data that can be reviewed and compared.

Search strategy:
We searched the recognized database like PubMed, Google Scholar, Science Direct, EMBASE and Cochrane library to identify studies eligible for this review. The primary key words for my research were thyroid abnormalities, Thyroid dysfunction, thyroid disorders, hypothyroidism, Hashimoto's thyroiditis, dementia, causes of dementia, AD, VD, Cognitive dysfunction, and cognitive impairment. The Boolean operators (AND, OR, NOT, AND NOT) were employed in order to combine or exclude key words in the search. We also searched the bibliographies of selected papers for additional studies. References of all the consulted studies are appropriately highlighted in this review. After the database search duplicate studies were removed. No consent forms obtained as it is a review of other research studies.

Inclusion & exclusion criteria:
Studies published in English language in last 20 years (2004-2024) and have scanned in depth the connection between hypothyroidism and dementia were included. Studies published outside the time frame and not in English, conference publications, case reports, animal studies or a letter to editor, studies with statistical errors were excluded from final interpretations.

Data Extraction: Data extraction completed by using a standardized form. Detailed information regarding the study year, author name, country of study, type of study, sample size, age of participants and final observations from each study were recorded. Figure 1 presents the search strategy flow chart. From database, 67 studies were identified. After excluding duplicates, 44 studies were selected for further assessment and 17 studies were finalized after reviewing abstracts of the remaining studies. Out of 17, Five studies can't be retrieved from database. Furthermore, 12 studies were assessed for eligibility and 3 out of them were again excluded due to various reasons like review article or conference abstracts, irrelevant information or outcome. I tried to contact the author of one included study where the full text was not available but was not successful in obtaining the full text.

No specific criteria for the diagnosis of dementia or hypothyroidism were considered in my systematic review for the selection process and all the criteria used by selected studies were accepted. In addition, if a study has explicitly reported the number of subjects diagnosed with hypothyroidism but failed to report the base of this diagnosis, these are included in my review.

Risk of Bias assessment: Risk of bias of selected studies was assessed according to the CASP (Critical Appraisal skills program) checklist of systematic reviews. It is a structured framework for critically appraising studies. This helps the user in being systematic by covering all the important factors and considerations. This checklist enables the user to assess the Validity, relevance and results of published papers.

Ethical Approval: The work is completed for MSc in Endocrinology from the University of South Wales UK and ethical committee has approved the proposal of project before starting the detailed work. The systematic review is not funded by any organization and there was no conflict of interest.

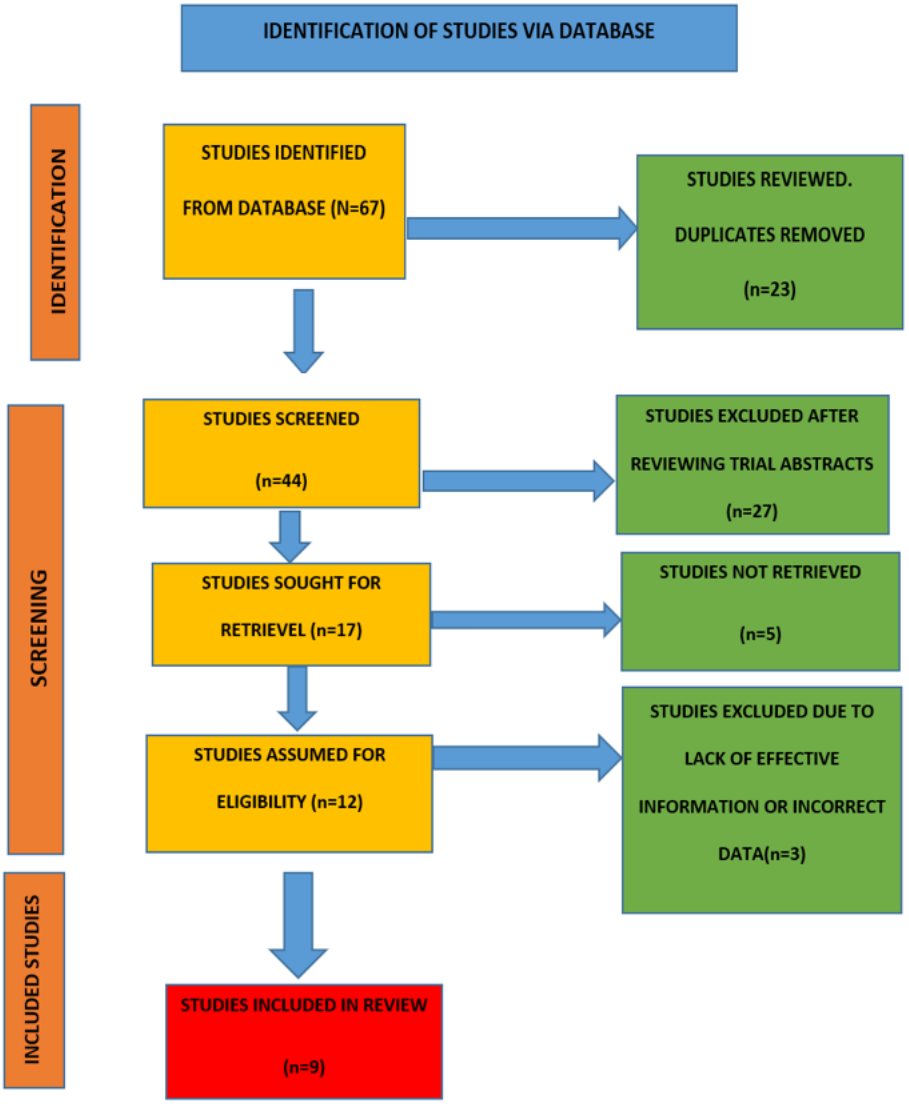

FIGURE: 1. Prisma flow diagram of literature search and article selection

RESULTS:

This systematic review included 9 studies covering 899,791 individuals. The earliest study was performed by Tan Z in 2008 (9) and the most recent studies were performed by Wieland et al (10) and Kim JH et al in 2022 (8). All the individual studies of this comprehensive review took place in different countries including Taiwan, Egypt, Korea, Denmark, India, China and Italy except done by Parsaik AK et al (11) and Aubert CE et al (12) which were conducted in USA. The predominant population of all these studies was found to be female. The sample size varied from 50 (Elbadawy 2020) (13) to 794,563 (Thvilum 2020) (14). The characteristics of included studies are summarized in Tables 1, 2, & 3.

Six of the nine studies included in this systematic review reported a clear association between hypothyroidism and dementia. In a nationwide population-based case-control study done on East-Asian subjects Wieland DR & co-workers (10) found that people aged ≥65 years with history of hypothyroidism and taking thyroid hormone replacement therapy were associated with 81% increased risk of dementia. Elbadawy & colleagues (13) described in 2022 that thyroid dysfunction especially subclinical hypothyroidism is associated with cognitive impairment. The risk of dementia increases with the increase in TSH while the MMSE score decreases with increasing age. Sample population were predominantly female (55% in cases and 80% in control). Serum TSH was significantly high and FT3 was low in patients in comparison to the control, but FT4 had no difference, p value is 0.03, 0.28 and 0.48 in order. In the studied groups 62.5% of patients had subclinical hypothyroidism, 7.5% had subclinical hyperthyroidism and 30% of the patients were euthyroid.

A conditional logistic regression was applied to estimate the relationship between thyroid disease and AD. It was reported that 602 patients (3.7%) had hypothyroidism, 599 patients were on levothyroxine

(3.6%), 591 patients (3.6%) had goiter, 280 patients (1.7%) had thyroiditis and 400 patients (2.4%) had hyperthyroidism. Subgroup analysis was performed to identify the incidence of thyroid disease in terms of age and sex (over 75 years of age or under; men or women) income and region of residence (low or high; urban or rural). Within each subgroup hypothyroidism, thyroiditis and hyperthyroidism were consistently associated with a higher likelihood of having AD. The study showed the prevalence rates of hypothyroidism (OR= 1.14, 95% [CI]=1.00-1.30), thyroiditis ([OR]= 1.22, 95% CI=1.05-1.40), and hyperthyroidism (OR=1.13, 95% CI= 1.01-1.28). These rates were found to be higher in participants with AD than in control population after adjustment with cofounders.

Thvilum M et al (14) analyzed in 2020 that hypothyroidism is associated with increased risk of dementia. This association is clearly governed by comorbid conditions and age of the patients. Every six months of increased TSH level increases the risk of having Dementia by 12%.

In OPENTHYPO cohort 79.3% were females and the median age at the time of first TSH measurement was 56.4 years for hypothyroid patients and 50.3 years for the reference individual. Both hypothyroid and reference population had same burden of morbidity as determined by CCI. This study amended that there is a higher prevalence of dementia among hypothyroid individual (3.7%) as compared to reference population (2.7%) and this association is strongly influenced by pre-existing morbidity and age. Bajaj S and colleagues (15) reported in 2014 that the prevalence of cognitive impairment was markedly higher in the patients of Subclinical hypothyroidism. Hu Y et al in 2016 conducted a case-control study on elderly participants in China and observed no significant association of cognitive impairment or dementia with hypothyroidism (16).

Table 1: Characteristics of Included Studies

Study	Year	Country	Type of study
Wieland	2022	Taiwan	Population bases case-control
Elbadawy	2022	Egypt	Case-control, cross-sectional, population based
Kim JH	2022	Korea	Case-control
Thvilum	2020	Denmark	Register based cohort study
Bajaj S	2014	India	Cross-sectional case-control study
Parsaik	2014	USA	Population based cohort study
Aubert	2017	USA	Population based prospective cohort
Hu Y	2016	China	Cross-sectional case control
Tan Z	2008	Italy	Longitudinal community based observational study.

Table 2: Observations from Included studies

Study	Observations
Wieland	>65 years old individuals with history of hypothyroidism have 81% increased risk of developing dementia.
Elbadawy	There is strong association between subclinical hypothyroidism and dementia. The risk of dementia increases with increase in TSH.
Kim JH	Hypothyroidism, hyperthyroidism and thyroiditis all increase the chances of having dementia.
Thvilum	There is increased risk of dementia in patients having hypothyroidism. Every 6months of increased TSH increase the risk of dementia by 12%.
Bajaj S	The prevalence of Cognitive impairment/dementia increases in patients of subclinical hypothyroidism.
Parsaik	Neither clinical nor subclinical hypothyroidism is associated with cognitive impairment/dementia.
Aubert	In elderly population, subclinical hypothyroidism or subclinical hyperthyroidism both are not related with development of dementia.
Hu Y	In old age Chinese population, there is no significant association of cognitive impairment/dementia with hypothyroidism.
Tan Z	Low or high TSH both are associated with increased risk of AD in females but not in males.

Table 3: Sample Sizes of included studies

Wieland	7843 cases, 7843 controls
Elbadawy	40 cases, 10 controls
Kim JH	16473 cases, 65892 controls
Thvilum	DNPR Cohort 111565 Cases and 446260 controls. OPENTHYRO Cohort 2894 Cases and 233844 controls
Bajaj S	103 Cases, 103 controls
Parsaik	1904
Aubert	2558
Hu Y	295 cases, 295 controls
Tan Z	1869

Discussion:

Dementia is a disabling clinical syndrome requiring new functional dependence on the basis of progressive cognitive decline. It is estimated that 1.3% of the entire UK population or 7.1% of those aged 65 or over have dementia (17). The incidence of dementia increases with age which makes it an increasingly common problem among the ageing population. The most prevalent risk factors include older age, genetic factors (apolipoprotein E genotype), family history, education level, comorbidities including a variety of vascular related illnesses (18-21). Dementia still has no effective disease modifying treatment and thus its prevention has become very important. It is mandatory to identify risk factors and potentially reversible causes for the prevention of this debilitating disease (22, 23).

In recent past several experimental studies reported the significant association between thyroid disorder, cognitive impairment and dementia (24) . Thyroid dysfunction can cause a range of mood and cognitive disturbances, especially in severe cases, including anxiety, depression, irritability, and deficit in executive function (5). Considering the significance, we aim to define the relationship of hypothyroidism and dementia in this systematic review, as hypothyroidism being the modifiable risk factor can reduce the prevalence of dementia in elderly population.

According to Flanagan EP (25), there can be 2 processes by which thyroid disorders may be associated with dementia. Action of abnormal thyroid hormone concentrations (high TSH causing low FT4 or high FT4 causing low TSH) on the brain causing impairment or autoimmunity causing AITD and encephalopathy leading to permanent brain damage. Reddy V et al in 2017 (26) described that long term exposure of the thyroid hormone can lead to cardiovascular and cerebrovascular diseases such as atrial fibrillation and systolic hypertension which are both directly linked with the risk of having Dementia.

In my systemic review I tried to investigate the relationship between hypothyroidism, cognitive status, and dementia. Six out of Nine studies showed a very clear association of hypothyroidism with dementia and cognitive dysfunction while 3 studies were failed to show any association. In the SADEM study, Juarez-Cedillo T et al (27) explained the relationship of thyroid disorder with cognitive decline which was much obvious in overt Hypothyroidism (OR=1.261). It was evaluated with Mexican elderly population. Baladini et al (28) in 1997 also found an association between cognitive impairment and subclinical hypothyroidism. This was concerted by Riben C & colleagues (29) in 2016 who analyzed that the risk of dementia is directly proportional to the level of TSH. Cook SE (30) reported in 2002 in a small scale study that older population with subclinical hypothyroidism performed worse than Euthyroid individuals. They were tested by immediate and delayed verbal recall and on the Mini-mental state examination. Chen Z (31) in 2016 showed a positive correlation of FT3 whereas negative correlation of TSH with mini-mental state scores in subcortical ischemic vascular dementia patients which has been proposed as a subtype of vascular cognitive impairment (VCI). Hence their results suggested that thyroid functions particularly hypothyroidism (increased TSH) was associated with cognitive impairment induced by SIVD.

In a small-scale study, Correia N & colleagues (32) in 2019 suggested that cognitive impairment occurs in subclinical hypothyroidism and more markedly in overt hypothyroidism. They also proposed that these deficits may result due to underling disruption of normal hippocampal function and/or connectivity. Hogervorst E (33) published their study in 2008 and reported that high TSH levels indicative of hypothyroidism were related significantly with lower global cognitive function (as measured with MMSE). In participants without overt thyroid disorders, high normal FT4 levels had a negative association with cognitive function at baseline. Some

interventional studies like Nystorm E (34) and Jaeschke R (35) reported improvement in cognitive function in subclinical hypothyroidism after administration of L-Thyroxine. Nystorm et al sample size was only 20 women while Jaeschke et al sample size was 37 patients. Hence, indirectly their studies favor that hypothyroidism is related to dementia.

However, on the contrary, some previous studies have not showed any interconnection between cognitive impairment or dementia and hypothyroidism (overt / subclinical) as observed in studies conducted by Hofman A (36), Roberts LM (37), Jorde R (38), Osterweil D (39), and Beno G (40). All reported that subclinical hypothyroidism hardly affects cognitive functions but it may have caused an age-related decline of attentive function. On the other hands, after 6 months of thyroid replacement treatment verbal fluency and depression scores showed a slight improvement. Although in previous studies, there was no direct evidence found that the decreasing TSH was improving the cognitive function but even then, Beno G recommended treatment of asymptomatic mild hypothyroidism in older subjects to protect the brain against the potential risk of cognitive and affective dysfunction.

In our systemic review, the most important factor identified is the age of the participant; with increasing age hypothyroidism association with dementia (cognitive dysfunction) increases. It appears that the neurons of elderly population are more vulnerable to thyroid alteration, and compensated euthyroid state may not reinstate all the domains of cognitive impairment caused by thyroid dysfunction. The second important observation of this review is the association of duration of hypothyroidism with severity of dementia. If the patients are taking thyroid replacement therapy due to hypothyroidism of any cause, their chances of having dementia increases to many folds. Duration of increased TSH levels also seems to play an important role in the development of dementia. The risk of dementia tends to rise 12% with every 6 months of increased TSH level.

Limitations of this review:

This systematic review produced valuable information regarding association between hypothyroidism and/or thyroid dysfunction with the risk of dementia. But as it is just the review of the studies, it contains cumulatively all the limitations which each of the individual study has, which must be considered while interpreting the results. Some limitations are outlined here. Firstly, Studies found on the association of hypothyroidism with the risk of developing dementia are very few. Although we have included large scaled studies conducted in different geographical areas of the world but still additional reliable evidence is required to clarify this relationship. Secondly, this analysis showed significant heterogeneity. It may be due to differences in sample size, methodological quality, demographic and racial characteristics, various covariate assessment and follow up duration.

Conclusion:

It has been found that hypothyroidism is related to marked changes in cognitive functions causing dementia and this association is directly proportional to increase in age, duration of hypothyroidism, and increase in TSH level. It is imperative to prioritize early detection and management by evaluating thyroid functions in individuals at a higher risk of developing cognitive decline or dementia.

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