

Thyroid Dysfunction and Its Role in Neurodegeneration: An Underestimated Synergistic Factor?

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OBJECTIVE

To quantify the prevalence of thyroid dysfunction across major neurodegenerative diseases and vascular dementia, and to assess sex differences evaluating whether thyroid dysregulation acts as a synergistic factor in neurodegeneration.

BACKGROUND

The contribution of thyroid dysregulation to neurodegenerative disease and abnormal aging remains insufficiently understood.

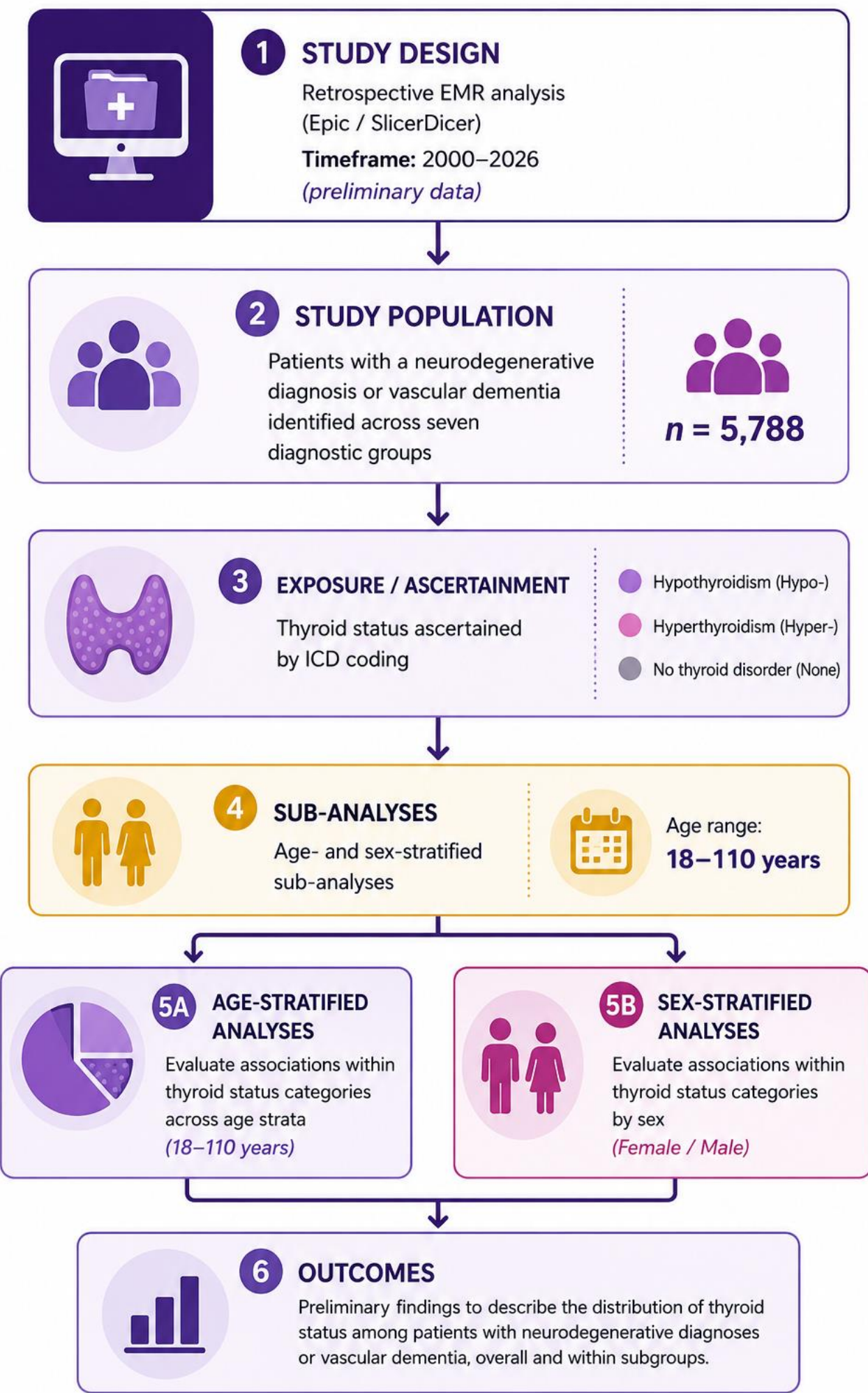
Thyroid hormones (TH) are essential for neuronal development, maturation, and homeostasis, and regulate proteins in apoptotic pathways.

TH imbalance may cause oxidative stress, mitochondrial dysfunction, and microglial disturbances that shift immune responses toward a pro-inflammatory M1 phenotype.

Low TH levels may contribute to neurodegeneration — particularly AD — by impairing ROS clearance, increasing amyloid- β accumulation, promoting tau phosphorylation, and enhancing hippocampal vulnerability to apoptosis.

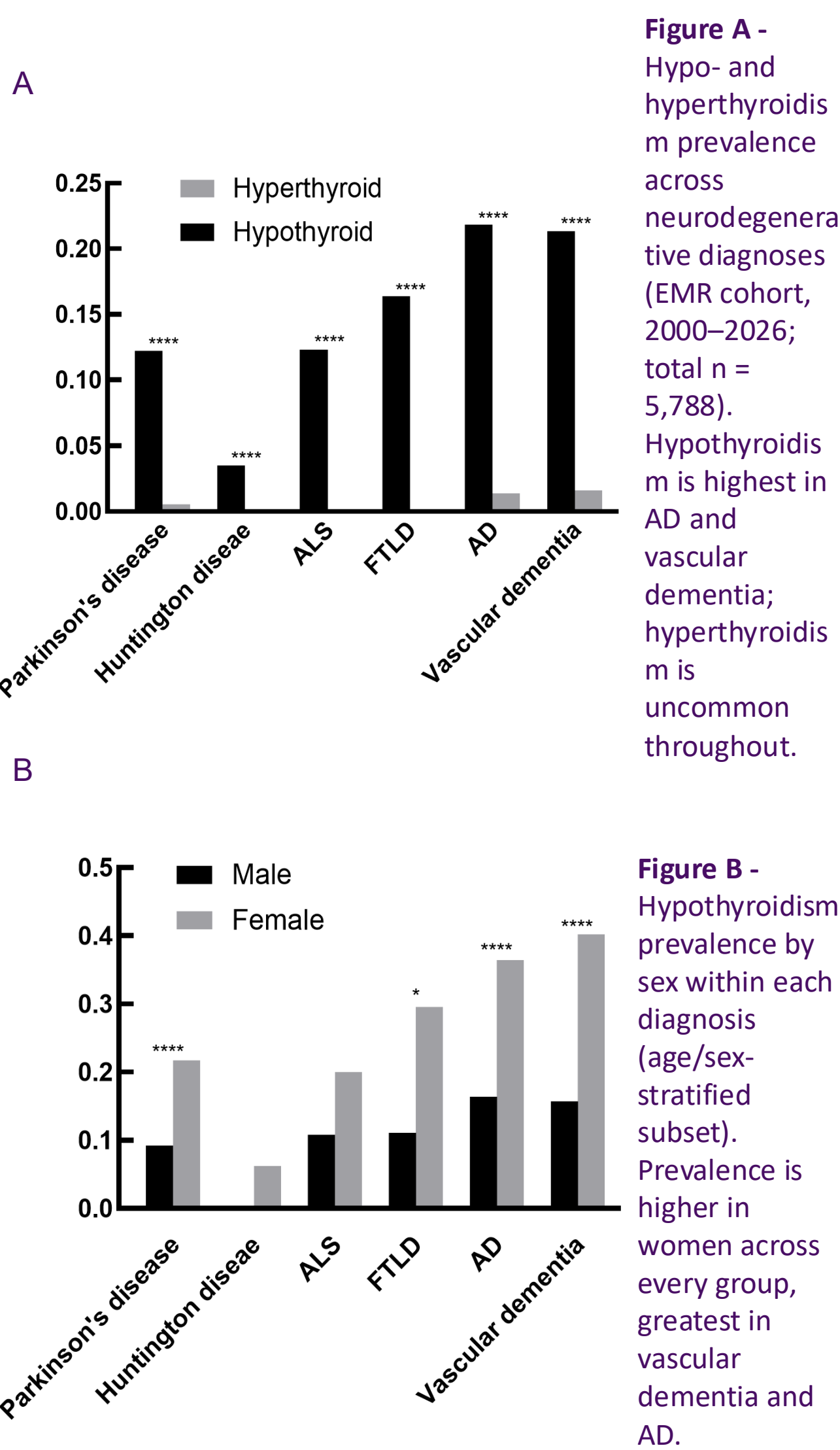
TH is also critical to the neurovascular unit functions

METHODS



Limitations: thyroid disease subtypes -including subclinical hypothyroidism and post-ablative hypothyroidism- inconsistently coded in EMR, and pending larger cohort analysis (ongoing)

RESULTS



CONCLUSIONS

Hypothyroidism concentrated in AD and vascular dementia

TH have been associated with modulating neurovascular metabolism and endothelial function, with a critical role in oxygen consumption and maintaining basal metabolic rate

Even mild hypothyroidism may disrupt the neurovascular unit and shift microglial immune responses toward a pro-inflammatory state

Previous studies have shown increased hippocampal neuronal apoptosis in hypothyroid patients

The marked female predominance of hypothyroidism, greatest in AD and vascular dementia, position TH dysfunction and particularly hypothyroidism as a potentially modifiable, sex-differential synergistic factor in neurodegeneration.

As a retrospective EMR prevalence analysis, temporality or causality cannot be established and more studies are necessary to determine whether TH dysfunction precedes, co-occurs or follows neurodegenerative diagnosis.

More data is needed to better understand the place of TH dyshomeostasis in neurodegeneration, neurovascular unit and microglia functions

CONCLUSIONS

Larger prospective cohort studies incorporating direct TH assays (TSH, fT4, fT3, rFT3) and longitudinal cognitive outcomes are warranted to establish causality and inform best screening, interventions and treatments.

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