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🌐 Impact of Higher versus Lower dose Levothyroxine treatment on Vascular and Bone Health in Older People with Hypothyroidism: protocol for an Emulation of a Target Trial

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Abstract

Background: Levothyroxine (LT4) is the standard treatment for hypothyroidism, but the optimal dosing for older adults remains unclear. Both higher and lower doses of LT4 may have differential effects on cardiovascular and bone health, with potential risks in ageing populations. We plan an emulated target trial aimed at assessing the impact of lower versus higher LT4 doses on cardiovascular events and bone health outcomes in older individuals with hypothyroidism.

Methods: We will utilise real-world data from a large, observational cohort of older adults with hypothyroidism residing in the United Kingdom from the Primary care-based THIN (The Health Improvement Network) electronic health records database. We will emulate a randomised trial comparing lower (≤ 1.0 $\mu\text{g/kg/day}$) versus higher (> 1.0 $\mu\text{g/kg/day}$) LT4 doses. The primary outcomes will be vascular events (including myocardial infarction, stroke, and heart failure) and bone health outcomes (fragility fractures or a diagnosis of osteoporosis). Secondary outcomes include all-cause mortality and healthcare utilisation rates. We will employ inverse probability of treatment weighting (IPTW) to adjust for relevant confounders and emulate randomisation. Cox proportional hazard models (weighted by IPTWs) will be used to estimate treatment effects on outcomes. The study period will be from 2006 to 2021, with follow-up durations ranging up to 10 years. Sensitivity analyses will be performed to confirm the robustness of the findings.

Dissemination and ethics: No ethical approval is needed to use this retrospective anonymised database. The results will be disseminated during conferences and through publication in a peer-reviewed scientific journal.

Conclusions: This emulated target trial of observational data from Primary Care will evaluate if higher doses of LT4 are associated with increased risks of cardiovascular events and bone health events, as well as higher mortality, compared to lower doses. The findings of this research will provide valuable information on whether lower LT4 doses may be safe and efficacious in this population, balancing effective thyroid hormone replacement with minimized cardiovascular and bone health risks. Based on the results of this research, further randomised trials will be planned to confirm these results and guide clinical practice.

Introduction

- 1 Hypothyroidism, a condition where the thyroid gland produces insufficient amounts of thyroid hormones, is common among older adults.¹ Hypothyroidism is more common in older people due to the natural decline in thyroid function with age, as well as other contributing factors such as the increased prevalence of autoimmune diseases (such as Hashimoto's thyroiditis) and treatment for hyperthyroidism.² The standard treatment for hypothyroidism is levothyroxine (LT4), a synthetic form of the thyroid hormone thyroxine.^{3,4} In general, studies show that LT4 use increases significantly with age, especially in people over 75, where the proportion can be closer to 20% or higher in some populations.^{5–7}

LT4 therapy aims to normalise thyroid hormone levels, alleviate symptoms of hypothyroidism and prevent long-term complications of hypothyroidism.³ Insufficient treatment is associated with adverse cardiovascular events, whereas excessive dosing may be related to a higher risk of cardiac arrhythmia and osteoporosis.⁸ However, the optimal dose of LT4 for older adults—particularly in terms of balancing vascular and bone health—remains unclear.

As individuals age, the body's response to thyroid hormones changes. Older adults may have altered metabolism, reduced renal clearance of thyroid hormones, and increased sensitivity to hormone fluctuations.⁹ These factors necessitate careful dosing of LT4 to avoid over- or under-treatment. The "right" dose must not only normalise thyroid function but also consider the delicate balance between maintaining vascular and bone health.

Thyroid hormones play an important role in cardiovascular function.¹⁰ Higher doses of LT4 can increase heart rate and blood pressure, and promote a hypermetabolic state, all of which may contribute to the development of cardiovascular conditions in older individuals. Studies have suggested that higher thyroid hormone levels—especially in individuals over the age of 65 years—are associated with an increased risk of atrial fibrillation, a condition that predisposes patients to stroke and heart failure.^{11–14} Moreover, excessive thyroid hormone can accelerate atherosclerosis, raising concerns that high-dose LT4 could increase the risk of cardiovascular events in this age group.¹⁵ On the contrary, lower doses of LT4 are less likely to induce these harmful cardiovascular effects.

Higher doses of LT4 may have a detrimental effect on bone density, particularly in older adults. Research has shown that overtreatment with LT4 can accelerate bone resorption, leading to decreased bone mineral density and an increased risk of fractures.^{16,17} This

effect is most pronounced in individuals who have low oestrogen levels (e.g., postmenopausal women) or those with other risk factors for osteoporosis.¹⁸ In contrast, lower doses of LT4 are less likely to cause bone loss. Maintaining a euthyroid state with a lower, more controlled dose of levothyroxine may help preserve bone mass and reduce the risk of fractures.

The “ideal” dose of treatment with LT4 in older people with hypothyroidism remains unclear. The goal of LT4 treatment in older individuals is to maintain a safe and balanced euthyroid state that minimises the risk of negative cardiovascular and skeletal outcomes. We, therefore, plan to explore the effects of higher versus lower doses of LT4 on vascular and bone outcomes in older individuals with hypothyroidism, shedding light on potential risks and benefits for this vulnerable population.

Methods

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Study Design

This study will utilise an emulated target trial design to compare the efficacy and safety of higher versus lower dose LT4 in older patients with hypothyroidism. An emulated target trial design allows for the use of observational data to mimic the randomisation and prospective follow-up of a randomised controlled trial (RCT). This approach is particularly suitable for studying interventions in populations where RCTs may be impractical or currently not planned. The target trial aims to assess the effects of different LT4 doses on vascular (angina, myocardial infarction, heart failure, stroke, peripheral vascular disease, atrial fibrillation, coronary revascularisation, coronary angioplasty) and bone health (fragility fractures, diagnosis of osteoporosis) outcomes in older individuals, aged above 50 years, diagnosed with hypothyroidism. The Hernan and Robins framework was adhered to for this study, to provide an overview of the study protocol (Table 1).

	A	B	C
	Protocol Components	Target Trial (ideal RCT)	Trial Emulation using observational data
	Eligibility criteria	· Adults aged over 50 years on January 1, 2006. · Patients with a primary hypothyroidism diagnosis. · Patients prescribed LT4.	Similar to the target trial and additionally: · At least 6 months of follow-up data available. · Initiation of LT4 therapy within the observation period. · Availability of at least one baseline thyroid stimulating hormone (TSH) and body weight

A	B	C
		measurement before therapy. · No history of contraindications (e.g. pituitary disease), other thyroid conditions, or thyroid treatment. · No use of drugs that affect thyroid function during the study period.
Treatment strategies	1. Patients who initiate LT4 at a dose >1mcg/kg/day. 2. Patients who initiate LT4 at a dose ≤1mcg/kg/day.	Same as the target trial.
Assignment procedures	Participants would be randomly assigned to either strategy at baseline and would be aware of the strategy to which they were assigned.	Randomisation will be emulated via inverse probability of treatment weighting (IPTW), using baseline and time-varying confounders.
Follow-up period	Start at randomisation and end at death, outcome event, or 10 years.	Start at baseline (initiation of LT4) and end at death, outcome event, administrative censoring, or 10 years.
Outcome	Vascular, bone health or mortality event within 10 years of baseline.	Same as target trial.
Causal contrasts of interest	Intention-to-treat principle. Expected estimand: the effect of being assigned to each intervention.	Observational analogue of the intention-to-treat principle.
Analysis plan	Cox proportional hazard models (one for each outcome event type: vascular, bone health, and mortality).	Same as target trial, except that observations will be weighted with IPTW.

Table 1 Overview of the target trial and trial emulation study protocols to estimate the effect of levothyroxine dose per body weight on vascular, bone health and mortality outcomes.

Study Population

The target population for this emulated trial consists of older adults (>50 years) with diagnosed hypothyroidism. Eligible participants must have been initiated on LT4 therapy for the management of hypothyroidism and have available baseline data on thyroid function tests, and vascular and bone health conditions. We will exclude individuals prescribed LT4 for other indications apart from primary hypothyroidism, such as pituitary disease, or previous treatment for hyperthyroidism or thyroid cancer.

Eligibility criteria

Inclusion criteria:

1. Age >50 years.
2. Diagnosis of primary hypothyroidism, confirmed by ICD-10 code.
3. Initiation of LT4 therapy within the observation period.
4. Availability of at least one baseline thyroid stimulating hormone (TSH) measurement before therapy.
5. Availability of at least one body weight measurement during the study period.

Exclusion criteria:

1. History of thyroid cancer, hyperthyroidism or pituitary disease.
2. Use of antithyroid drugs, liothyronine or medications affecting thyroid function (such as lithium or amiodarone) during the study period.
3. Previous thyroid surgery or radioiodine treatment.
4. Pre-existing vascular conditions or bone disease, for each outcome assessment.
5. Insufficient length of follow-up (< 6 months).

Intervention and Comparator

The two primary exposures in this emulated target trial are:

1. **Higher Dose LT4 Group:** Participants in this group will receive an LT4 dose >1mcg/kg/day at baseline.
2. **Lower Dose LT4 Group:** In this group, participants will receive LT4 at a dose of ≤1mcg/kg/day at baseline.

The causal contrasts of interest will be an intention-to-treat effect. The LT4 dose cut-off to define higher or lower dose was decided based on data from the Baltimore Longitudinal Study of Aging, which assessed LT4 dose per actual body weight per day in participants aged 65 years or older on LT4 therapy for primary hypothyroidism.¹⁹ This study found that the mean dose of LT4 needed to maintain euthyroidism was 1.09 mcg/kg/day. Thus, we will use 1.0 mcg/kg/day of LT4 dose to stratify our intervention and comparator groups.

Data Sources

The vast majority of patients with primary hypothyroidism are managed in Primary Care. This study will obtain data from a large, established cohort database (The Health Improvement Network or THIN) that includes comprehensive information on thyroid function tests, LT4 prescriptions, and outcomes related to vascular and bone health. THIN captures clinical data from general practices across the UK, holding anonymised records of approximately 6% of the UK population from 850 general practices.²⁰ This database has been utilised previously to retrospectively study the association between LT4 therapy, serum TSH concentrations and long-term health outcomes.⁸ THIN has over 25 years of data recorded. To ensure a complete and reliable dataset, this project will capture data between January 1st, 2006, and December 31st, 2021. We will extract baseline characteristics, thyroid function test results, comorbidities,

concomitant medications, and demographic information to emulate the trial design. Preliminary counts from THIN indicate that 9,633 patients aged over 50 years, who are prescribed LT4, have both weight and TSH value above 4.0 mU/L recorded in the database.

Outcome Measures

The primary and secondary outcomes will be assessed through a combination of clinical assessments and laboratory tests. Search terms will be focused on International Classification of Diseases Tenth Revision (ICD-10) codes: E03 for hypothyroidism, E05 for hyperthyroidism, C73 for thyroid cancer, E22-E24 for pituitary disease, I20 for angina, I21-I23 for myocardial infarction, I60-I64 for stroke, I70-I79 for peripheral vascular disease, M80-M81 for osteoporosis, and M84.4, S32, S52.5, or S62 for fragility fractures. Codes relating to Raynaud's disease, vibration syndrome, hereditary diseases, naevus, telangiectasia, post-radiological, or Williams-Campbell syndrome will be excluded from peripheral vascular disease codes. Also, fractures on digits or pathological fractures will not be included in the search for fragility fractures. Notably, ICD-10 codes do not encompass treatments or surgery. Therefore, treatment terms were based on British National Formulary treatment names, and surgery terms were based on Read Codes. Notably, res12: percutaneous transluminal coronary angioplasty and res15: Coronary revascularisation code lists were searched for revascularisation outcomes.^{21,22}

Primary Outcomes:

1. **Vascular:** This includes a composite of major cardiovascular events such as new diagnoses of angina, myocardial infarction, stroke, peripheral vascular disease, revascularisation procedures (stenting or bypass grafting), heart failure and atrial fibrillation.
2. **Bone Health:** This will be measured by a new diagnosis of osteoporosis or the incidence of fragility fractures.

Secondary Outcomes:

1. **All-cause mortality:** This will be assessed by the relevant coding.
2. **Thyroid Function:** TSH and free T4, if available, will be monitored to assess the adequacy of LT4 dosing.
3. **Inappropriate treatment:** The proportion of individuals who had average serum TSH levels below and above the TSH reference range (0.3 – 4.5 mU/L) over the study period.
4. **Primary healthcare resource utilisation:** The average number of visits per year to the GP practice.

Exposure Assessment

The exposure to higher versus lower doses of LT4 will be based on medication dispensing data, including dose and frequency of prescriptions. We will consider the average dose over the study period, as well as adjustments made for thyroid function test results, to ensure accurate exposure classification. Patients will be followed for at

least 6 months, with longitudinal assessments of medication adherence, thyroid function, and health outcomes.

Follow-up

Participants will be followed from the initiation of LT4 (time zero) until:

- 1. First occurrence of a primary outcome event.**
- 2. End of study period.**
- 3. Death.**
- 4. Administrative censoring.**

There will be a 10-year follow-up for all participants recorded in the THIN database between January 1, 2006, and December 31, 2021. A minimum follow-up period of 6 months is required for all participants.

Statistical Analysis

We will use a time-varying approach to analyse the effects of LT4 dose on vascular and bone health outcomes, adjusting for baseline covariates and time-dependent factors.

The analysis will include the following steps:

- 1. Inverse Probability of Treatment Weighting (IPTW):** To emulate randomisation, we will use IPTW to balance baseline characteristics between the higher and lower dose groups, controlling for potential baseline and time-varying confounders such as age, sex assigned at birth, comorbidities (assessed by the Charlson Comorbidity Index (CCI), history of hypertension, serum TSH level, smoking, proton pump inhibitor (PPI) use, and concomitant hormonal medications (oestrogen and testosterone). Weights will be calculated at each time point using logistic regression models based on time-varying confounders. The predicted probabilities from the logistic regression models will be used to calculate weights that reflect the inverse probability of receiving the observed treatment at each time point. Stabilised weights will then be derived by incorporating the overall exposure treatment in the population. Weights will be truncated within the 1st and 99th percentiles. Confounders will be adjusted depending on the outcome variable (Table 2). All time-varying covariates will be updated daily, based on relevant prescriptions, ICD-10 codes and Read codes.
- 2. Cox Proportional Hazard Regression:** To analyse time-to-event outcomes, such as cardiovascular events or fractures, we will use Cox proportional hazard models to estimate the relative risk of these events between the higher and lower dose LT4 groups.
- 3. Sensitivity Analyses:** We will perform sensitivity analyses to assess the robustness of the results, including using different methods for handling missing data (e.g., multiple imputation) and varying covariate adjustment strategies. We will also assess the primary outcomes separately by sex assigned at birth, age groups (51-60, 61-70, 71-80, >80 years) and by lower and higher baseline serum TSH level ($\leq$ or > 10.0 mU/L). Furthermore, as statin use and hypertension may be mediators (rather than confounders)

of the relationship between thyroid function and cardiovascular events, we will analyse the data after excluding statin use and hypertension diagnosis from the model.

4. Time-varying covariates: Certain variables may vary over time and could influence the dose of LT4, such as changes in LT4 dose or body weight. We will, therefore, use time-varying analysis, with daily time points, to adjust for these factors.

A	B
Outcome	Confounding variables
Vascular	Age, sex assigned at birth, Charlson Comorbidity Index (CCI), serum TSH levels, hypertension, statin use, smoking status, proton pump inhibitor medications, and hormonal medications.
Bone Health	Age, sex assigned at birth, CCI, serum TSH levels, hypertension, statin use, smoking status, proton pump inhibitor medications, hormonal medications, and anti-epilepsy medications.
All-Cause Mortality	Age, sex assigned at birth, CCI, serum TSH levels, hypertension, statin use, smoking status, proton pump inhibitor medications, and hormonal medications.

Table 2 Overview of the confounding factors between the use of levothyroxine and vascular, bone health and mortality outcomes.

Directed Acyclic Graph

A Directed Acyclic Graph (DAG) is a graph representing dependencies or relationships between exposure (LT4 dose per body weight) and outcome (vascular, bone health, mortality) variables. The below DAG diagram is a simplified diagram created based on current literature, clinical expertise and the published British National Formulary and National Institute for Health and Care Research Clinical Knowledge Summary guidelines (Figure 1). The online platform Daggity was used to create the diagram and identify required adjustments.²³

Figure 1 Directed Acyclic Graph illustrating the time-varying effects of levothyroxine (LT4) dose on vascular health, bone health, and mortality. Thyroid-stimulating hormone (TSH) is treated as a confounder, along with other confounders, including age, sex assigned at birth, comorbidities, hypertension, smoking, proton pump inhibitor medications, hormonal medications, cancer diagnosis, and anti-epilepsy medications.

Confounders are adjusted based on their relevance to each specific outcome. The model also accounts for unmeasured confounding. Numbers (0, 1, and 2) represent successive time points.

Ethical Considerations

This study does not require a National Health Service Research Ethics Committee review as the data is observational, retrospective and pseudonymised. The University of Sunderland Research Ethics Group has approved this study (application ID 011081). THIN scientific review committee has approved this study, protocol number 22-003.

Limitations

While an emulated target trial design is a powerful tool for leveraging observational data to simulate RCT-like results, limitations include the potential for residual confounding, particularly concerning unmeasured factors influencing both LT4 dosing and health outcomes. Additionally, the non-randomised nature of the trial means that treatment groups may still differ in ways not fully captured by inverse probability weighting. Similar to other observational studies that utilise large 'real-world' datasets, there is a potential for misclassification of variables or outcomes. In addition, the results from this analysis will be limited in their generalisability to populations similar to the data source.

Conclusion

- 3 This emulated target trial will provide valuable insights into the impact of higher versus lower doses of LT4 on vascular and bone health in older adults with hypothyroidism, with implications for optimising treatment strategies in this vulnerable population. The diagnosis of hypothyroidism is increasing, and LT4 prescriptions have been noted to be rising in both the USA and the UK. A significant proportion of older adults are treated with LT4 therapy. The long-term safety and efficacy implications of LT4 therapy in the older age group have not been elucidated.

Previous studies examining the association between levothyroxine use in older people and CV and bone health events have shown inconsistent results. An observational study of healthcare databases from Ontario, Canada, revealed a higher risk of atrial fibrillation with an LT4 dose of more than 75 mcg/day.¹¹ Another study from the same authors utilising similar databases concluded that LT4 treatment was associated with a higher risk of fractures, and importantly, there appeared to be a strong dose-response relationship.¹⁷ A study analysed the records from a UK General Practice database and found that LT4 prescriptions were associated with a higher risk of fractures in men only.²⁴ An analysis from the Korean Health Insurance database concluded that both high- and low-dose LT4 treatment was associated with a higher risk of fractures in a J-shaped dose-dependent manner in post-thyroidectomy thyroid cancer patients.²⁵ Using

the same Korean National Health Insurance database, researchers found a higher risk of coronary heart disease and ischaemic stroke, with higher doses appearing to be associated with increased risk.²⁶ An observational study of singletons and dizygotic twins discordant for hypothyroidism revealed that those affected with hypothyroidism had a higher all-cause mortality risk.²⁷ Studies that predominantly included younger people or only postmenopausal women have not found an association between fractures and LT4 use.^{28–30}

The results of previous studies are likely to be influenced by biases that are inherent in the design and analysis of observational studies.³¹ Causal inference requires the comparison of outcomes under different courses of action. The key advantage of a randomised controlled trial (RCT) is that both groups are expected to be comparable, and any difference in outcomes can be attributed to the intervention being studied rather than to prognostic differences between the groups. In addition, in an RCT, the start of follow-up (time zero) for each participant is specified (which is the time of randomisation), as is the assigned treatment group. However, these features are missing when drawing causal conclusions from observational data. One way to ensure that observational analyses preserve these desirable features of randomised trials is to design them so that they explicitly emulate a hypothetical randomised trial that would answer the question at hand: the *target trial*.³² The analysis we plan in this protocol is designed to emulate a trial of LT4 treatment in older people with hypothyroidism and assess CV and bone outcomes using real-world National Health Service data.

Target trials emulated with observational data are necessarily pragmatic trials. Explicit target trial emulation alone cannot eliminate the bias that arises from the lack of randomisation, even if the observational analysis accurately emulates all other aspects of the target trial. A successful target trial emulation requires detailed data not only on the treatment being studied and the outcomes of interest but also on the confounders. The biggest advantage of a correct target trial emulation is that it mitigates other common sources of bias so that confounding can be addressed. Furthermore, an emulated target trial cannot include blinded treatment assignment (e.g., using a placebo control) and blinded outcome ascertainment because these are not routinely performed in clinical practice (32).

In conclusion, this study will perform an emulated trial of LT4 treatment using clinical data from a large number of patients and assess the relationship of the dose of LT4 with important vascular and bone outcomes as well as all-cause mortality and health care resource utilisation. The results of this study, which will need to be confirmed in appropriately designed prospective randomised trials, have the potential to fundamentally alter clinical practice affecting a large proportion of older people.



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