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Exploring symptoms and signs of mild thyroid overactivity in Dutch primary care

Submission date
11/05/2023

Recruitment status
No longer recruiting

Registration date
25/05/2023

Overall study status
Completed

Last Edited
28/10/2024

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol
Background and study aims
The aim of this study is to determine how many people in the Netherlands have or develop a condition called subclinical hyperthyroidism and whether they have a higher risk of negative health outcomes, such as fractures or cardiovascular disease. Subclinical hyperthyroidism is when you have low or undetectable thyroid-stimulating hormone (TSH) levels with normal thyroid hormone levels.

Who can participate?
Adults with subclinical hyperthyroidism and adults without thyroid disorders. Data from medical records will be used from the PHARMO database (https://pharmo.nl/).

What does the study involve?
Medical records will be compared between people with subclinical hyperthyroidism and people with normal thyroid function.

What are the possible benefits and risks of participating?
There are no direct benefits or risks to patients whose medical records are included.

Where is the study run from?
Amsterdam University Medical Centers (Amsterdam)

When is the study starting and how long is it expected to run for?
December 2022 to June 2025

Who is funding the study?
Amsterdam University Medical Centers (Netherlands)

Who is the main contact?
1. Dr. Stan Ursem, s.ursem@amsterdamumc.nl
2. Prof. Annemieke Heijboer, a.heijboer@amsterdamumc.nl

Contact information

Type(s)
Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
P2365

Study information

Scientific Title
Subclinical hyperthyroidism and TSH measurements in primary care in the Netherlands

Study objectives
For this observational study, the aim is to investigate the prevalence and incidence of endogenous subclinical hyperthyroidism in the Netherlands in primary care. In addition, the researchers want to assess the natural course, as well as the risk for adverse health outcomes and comorbidities, of patients with subclinical hyperthyroidism in primary care. Hypotheses will be generated using exploratory analysis described under "Intervention".

Ethics approval required
Old ethics approval format

Ethics approval(s)
This is an anonymized retrospective observational study, which does not require ethics approval under the Dutch law "Wet medisch-wetenschappelijk onderzoek met mensen" 1998. The study has been assessed by the Compliance Committee of PHARMO (https://pharmo.nl/).

Study design
Observational nested case-control study

Primary study design
Observational

Secondary study design
Nested case-control study

Study setting(s)
GP practice

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Subclinical hyperthyroidism

Interventions
A dataset will be extracted from the PHARMO general practitioner database (see https://pharmo.nl/) using routine care data. A nested case-control study will be performed. For every case (see inclusion criteria below), four matched controls are included based on age, sex and general practitioner practice.

The incidence and prevalence of patients with subclinical hyperthyroidism (SHT) will be compared with the total number of patients with a TSH measurement. Over the years 2010-2021 the researchers want to assess the yearly incidence and prevalence of SHT against the total group of requested TSH measurements (with exclusion criteria applied). For this research question they would not require a dataset.

For the other hypotheses the researchers will use a dataset over the last 10 years (2012-2022) to compare a group of patients with SHT and a group of euthyroid patients.

First, 25% of the dataset will be used for exploratory analyses and researchers will not have access to the other 75%. After determining hypotheses and establishing an analysis protocol, confirmatory analyses will be performed on the other 75% of the dataset.

Differences in proportions between groups (e.g. subclinical hyperthyroidism vs euthyroidism) will be investigated with Chi-square tests (categorical data) and independent t-tests (normally distributed continuous data) or Mann-Whitney U tests (not normally distributed data). Associations between subclinical hyperthyroidism and clinical outcomes (atrial fibrillation, coronary artery disease, heart failure, osteoporosis, fractures, stroke, dementia and mortality) will be investigated with time-to-event analyses (e.g. Cox proportional hazard models and competing risk analysis). Primary analyses will be adjusted for sex and age (since some traditional risk factors may be potential mediators), and then for traditional risk factors, i.e. diabetes, pre-existent cardiovascular disease and medications (lipid-lowering, antihypertensive or anti-osteoporosis treatment).

Intervention Type
Other

Primary outcome measure
Cardiovascular comorbidity and bone health. In the exploratory analyses the exact outcomes will be determined by means of International Classification of Primary Care (ICPC) codes, medication use (such as osteoporosis medication or medication used in heart failure) and relevant laboratory data (for example cholesterol and BNP values), the researchers will compare this comorbidity between the subclinical hyperthyroid group and controls using a dataset over the last 10 years (2012-2022).

Secondary outcome measures
Natural course of subclinical hyperthyroidism by TSH and free T4 concentrations using a dataset over the last 10 years (2012-2022)

Overall study start date
16/12/2022

Completion date
01/06/2025

Eligibility

Key inclusion criteria
Cases: Patients with TSH concentration below reference range and with fT4 concentration within reference range (at same measurement) or patients with recorded ICPC code A91.07 (subclinical hyperthyroidism).

Controls: TSH and fT4 measurement within reference range

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
>200

Key exclusion criteria
Cases:
1. In 2 years prior to inclusion use of amiodarone (ATC C01BD01)
2. In 2 years prior to inclusion use of thyroid medication (ATC starting with H03)
3. Ever recorded use of lithium (ATC N05AN01)
4. In 2 years prior to inclusion mention of ICPC T85 (hyperthyroidism), T86 (hypothyroidism), A91.07 (subclinical hyperthyroidism), T71 (thyroid malignancy), A91.06 (subclinical hypothyroidism)

Controls:
During 5-year follow-up from cohort entry date:
1. TSH or FT4 measurement outside of reference range
2. Mention of ICPC codes (see also above) T85, T86, A91.07, T71, A91.06

Date of first enrolment
01/01/2012

Date of final enrolment
31/12/2021

Locations

Countries of recruitment
Netherlands

Study participating centre
PHARMO institute
Van Deventerlaan 30-40
Utrecht
Netherlands
3528 AE

Sponsor information

Organisation
Amsterdam University Medical Centers

Sponsor details
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Sponsor type
Hospital/treatment centre

Website
https://www.amsterdamumc.org/research/institutes/cancer-center-amsterdam.htm

ROR
https://ror.org/05grdyy37

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Amsterdam University Medical Centers

Alternative Name(s)
Amsterdam UMC, Amsterdam University Medical Centres, AUMC

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Netherlands

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal and presentation at relevant scientific conferences.

Intention to publish date
01/06/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon reasonable request for scientific verifications or evaluation of the quality of the research via Dr Stan Ursem (s.ursem@amsterdamumc.nl). These data will be retained for at least 10 years. Personal data from participants cannot be shared and are also unknown to the authors. The other data (year of birth, comorbidity, laboratory data and medication) are available for the above-mentioned requests. PHARMO will be informed of such a request for peer review.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	Protocol and SAP CVD	27/10/2024	28/10/2024	No	No
Protocol file	Protocol and SAP natural course	27/10/2024	28/10/2024	No	No

Statistical Analysis Plan	Protocol and SAP Bone	27/10/2024	28/10/2024	No	No