5. Research Progress

Short Introduction of my PhD Project

Mild degrees of thyroid dysfunction are common in the general population, especially among the elderly [1]. Patients are usually diagnosed with subclinical thyroid dysfunction (SCTD) if their serum thyroid stimulating hormone (TSH) levels are either abnormally high or low but their serum-free thyroxine (ft4) is normal. If their TSH level is high, they are diagnosed with subclinical hypothyroidism (SHypo) or, if it is low, with hyperthyroidism (SHyper) [1]. An SCTD diagnosis may be associated with several negative health outcomes; depression is one of them. In subclinical hypothyroidism, the presence of depressive symptoms is often a reason for starting levothyroxine treatment [2].
Studies that have explored the association between subclinical thyroid dysfunction (SCTD) and depressive symptoms have shown conflicting results [3-6], in part due to inconsistencies in definitions of SCTD and cut-off levels. A recent meta-analysis of four RCTs (n=278) found no benefit of levothyroxine therapy on depressive symptoms in patients with subclinical hypothyroidism [7]. However, this meta-analysis included only 278 participants, resulting in a confidence interval that does not exclude a small clinical benefit of levothyroxine. For my PhD project, I have two aims. The first aim is to conduct an individual participant data (IPD) meta-analysis of relevant studies to identify the association between SCTD and depressive symptoms. My second aim is to assess the impact of levothyroxine therapy on depressive symptoms in individuals with SHypo, using unpublished data from the TRUST trial.

Progress Aim 1

So far, I am well on the schedule with the timetable on the project form submitted with the GHS application. I completed the systematic literature research in MEDLINE and EMBASE, Cochrane Library, and Cinahl, I requested individual participant data from the Thyroid Studies Collaboration (TSC) and finished the analyses and submitted the article (Status: submitted)

I made some improvements to the research plan submitted for the GHS application. First, additionally to the association between subclinical hypothyroidism (SHypo) and depressive symptoms I did analyse the association between subclinical hyperthyroidism (SHyper) and depressive symptoms. Second, to be able to better interpret the results, I decided to convert all the scores measured with different depressive symptoms scales to the Beck Depression Inventory Scale instead of using a standardized scale from 0 to 1. For aim 1, I defined a primary and secondary outcomes (see below). For Aim 1 I included the question if the incidence of depressive symptoms is higher in SHypo or SHyper compared to euthyroid control.

Aim 1, Primary outcome:

- Depressive symptoms measured on a continuous scale at the first individual available follow-up.

Aim 2, Secondary outcomes:

- Depressive symptoms measured on a continuous scale *(a)* at a specific follow-up time point (after year 3 FUP) and *(b)* at the last available individual follow-up.
- Incident depressive symptoms during follow-up (Dichotomous outcome: proportion of participants with scores higher than validated cut-off or Incident depressive symptoms measured with ICD diagnosis) *(a)* at the first individual available follow-up *(b)* at a specific follow-up (e.g. year 3 follow-up) *(c)* at the last available individual follow-up.

Results Aim 1

I identified 11 prospective cohort studies that met the inclusion criteria. Ten studies agreed to participate and provided individual participant data. One big study (220'545 participants) did not reply to our request several times, so we had to decide to exclude this study. Three studies have no baseline data on depressive symptoms. One study measured depressive symptoms not on a continuous scale. Here I present results for the primary outcome including six studies with available data on depressive symptoms measured on a continuous scale at baseline and follow-up.

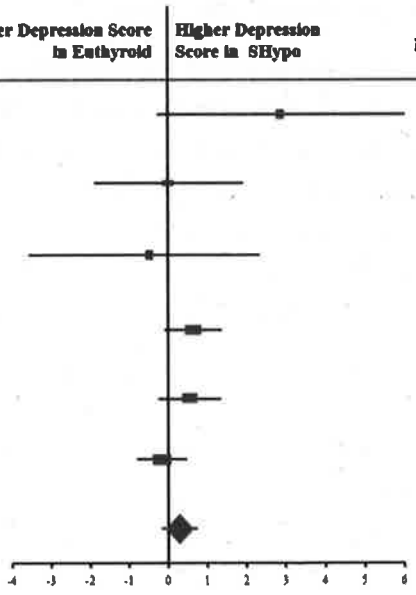
Among six cohorts, we analyzed data from 23038 participants (65% female, mean age 60 years, SHypo N=1342, SHyper N=671). At baseline there was no relevant difference in depressive symptoms between euthyroid participants (mean BDI = 10·28) and participants with subclinical hypothyroidism (mean BDI = 9·63). At first available follow-up (mean 8·2 (±4·3) years), there was no difference in the primary outcome of BDI score between subclinical hypothyroidism and euthyroid controls (pooled mean difference (MD) 0·29, 95% CI -0·17 to 0·76) with a low heterogeneity (I^2=15·6%) (Figure 1). There was also no relevant difference in the primary outcome of depressive symptoms between subclinical hyperthyroidism and euthyroid controls (MD 0·10, 95% CI -0·67 to 0·48, I^2 = 3·2%) at first available follow-up (Figure 1). The results stayed robust in several sensitivity and subgroup analyses. There was also no difference in depressive symptoms between the groups for the secondary outcomes (at year 3, last follow-up, dichotomized analysis (incidence); Results not shown)

Figure 1:

Difference in BDI score between participants with subclinical hypothyroidism and euthyroid participants after the first available follow up*

Study	No. of Participants Euthyroid	SHypo	Higher Depression Score in Euthyroid	Higher Depression Score in SHypo	MD in BDI (95% CI)	Weight %
Leiden 85+	237	26			2·87 (−0·28, 6·02)	2·12
PROSPER	345	44			0·00 (−1·91, 1·92)	5·56
InChianti	866	25			−0·52 (−3·36, 2·31)	2·61
Health ABC	1910	272			0·60 (−0·13, 1·33)	29·07
CHS	2852	466			0·50 (−0·29, 1·30)	25·67
HUNT	14815	509			-0·17 (−0·81, 0·47)	34·96
Summary	**21025**	**1342**			**0·29 (−0·17, 0·76)**	**100·00**

Overall I^2 = 15·6 %, tau^2 = 0·05, Q = 5·93



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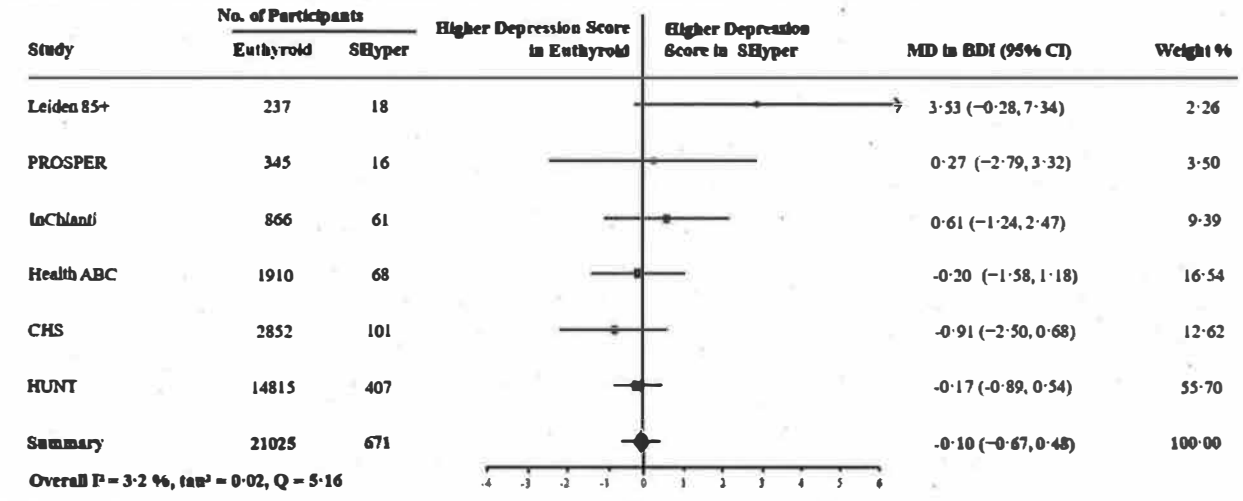
Difference in BDI score between participants with subclinical hyperthyroidism and euthyroid participants after the first available follow up*



** Analysis adjusted for depressive symptoms at baseline, sex, age, and education (The CHS, Health ABC Study, and the InChianti Study were additionally adjusted for income)*

Abbreviations: SHypo, Subclinical Hypothyroidism; SHyper, Subclinical Hyperthyroidism; Leiden 85+, Leiden 85 plus Study; PROSPER, Prospective Study of Pravastatin in the Elderly at risk; Health ABC Study, The Health, Ageing and Body Composition Study; CHS, Cardiovascular Health Study; InChianti Study, Invecchiare in Chianti Study; HUNT, Nord-Trøndelag Health Study; BDI, Beck Depression Inventory Score (range 0-63, minimal clinically important difference 5 points); MD, Mean Difference; CI, Confidence Interval, No., Number

Discussion Aim 1

The analysis of large prospective cohorts showed that, neither SHypo nor SHyper were associated with an increase in depressive symptoms. Since I could not find any association in the subclinical range, I will not analyse if there is a prospective association between TSH levels within the normal range and depressive symptoms. Our results are in contrast with the traditional notion that subclinical thyroid dysfunction, and subclinical hypothyroidism in particular, is associated with depressive symptoms. Consequently, our results do not support the practice of prescribing levothyroxine to treat depressive symptoms when they co-occur with subclinical hypothyroidism. Results should be confirmed using data from a RCT.

Outlook Aim 1

to add

Progress Aim 2

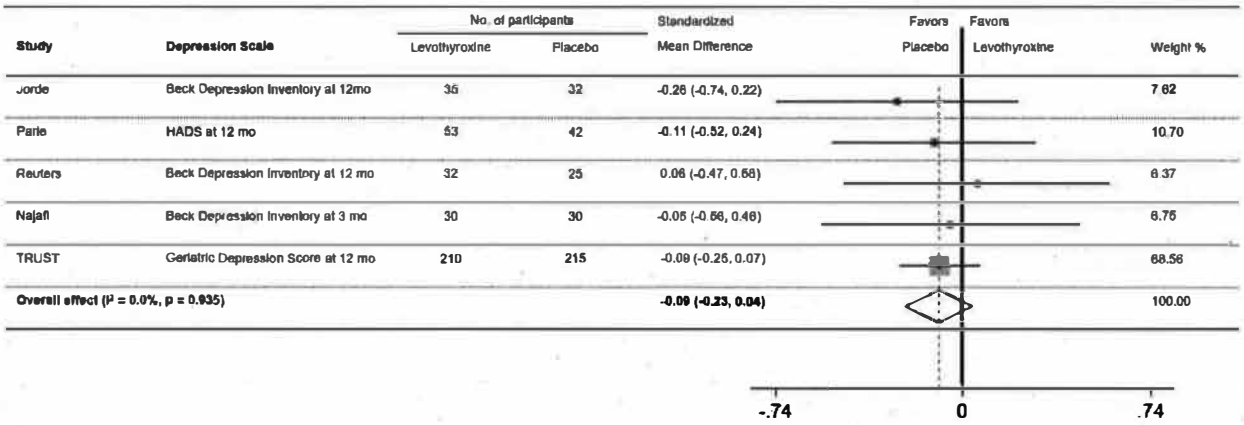
As determined in the timeline bellow I did request, prepared, and cleaned the data from the TRUST study for the second aim in the end of 2019. Two sides from the TRUST study measured depressive symptoms on the Geriatric Depression Scale (The Netherlands, Switzerland). To receive the data for this project I first had to write an analysis plan for the TRUST substudy on depressive symptoms, which was accepted in December 2019 from all the co-authors and the TRUST committee. After the data preparation, I conducted the main analyses and I started to write the manuscript. The main outcome of the study is defined as the mean difference in depressive symptoms at the 12-month follow-up. Additionally I conducted an update of the previous meta-analysis on the benefit of Levothyroxine treatment on depressive symptoms including the TRUST study.

Results Aim 2

The TRUST substudy on depressive symptoms includes 425 participants with subclinical hypothyroidism. 215 were randomized to the placebo and 210 to the levothyroxine group. At baseline the mean TSH was 6.55 mIU/Liter and there was no difference in depressive symptoms between the two groups. After 12 months follow up the TSH decreased to 3.81 mIU/L in the levothyroxine vs. 5.91 mIU/L in the placebo group. The mean GDS-15 score at 12 months was 1.4 (2.1) in the levothyroxine and 1.1 (1.7) in the placebo group with an adjusted between-group difference of 0.17 for levothyroxine vs. placebo (95% confidence interval:-0.14 to 0.48; p = 0.29).

The updated meta-analysis on the topic is shown in Figure 2. There was no clinical relevant difference in depressive symptoms between the placebo and Levothyroxin group on a standardized depression scale.

Figure 2: Meta-Analysis - Difference in depressive symptoms between Placebo and Levothyroxine group on a standardized scale



Conclusion Aim 2

In this by far largest RCT on the topic, levothyroxine therapy did not confer a benefit regarding depressive symptoms. Consequently, our results do not support the practice of prescribing levothyroxine for depressive symptoms when they co-occur with subclinical hypothyroidism.

Outlook Aim 2

to add

Additional project (3rd Publication as 2nd author)

Background: Levothyroxine prescriptions are rising worldwide. In 2014 Levothyroxine becomes the most prescribed drug in the USA and the third most prescribed drug in the UK [8]. However, for Switzerland we do not know the prevalence of chronic levothyroxine use.

Methods: For this reason, we assessed the prevalence of chronic levothyroxine use in a population-based cohort from Lausanne (CoLaus) and we cundcuted a ranking of most invoiced drugs using insurance data from Switzerland.

Results: In the cohort from Lausanne (CoLaus), Levothyroxine was the second most prescribed chronic drug after aspirin (8.2 %). When the 30 most used chronic drugs from the CoLaus cohort were ranked using 2018 invoice data from SantéSuisse, levothyroxine was third after aspirin and calcium-vitamin D.

Outlook Aim 3

I plan to submit an abstract on the results from the TRUST substudy on depressive symptoms to the SGAIM meeting *(Meeting der Schweizerischen Gesellschaft für Allgemeine Innere Medizin in Basel)* in June and to the Swiss Public Health Conference in August this year. According to the timetable, I plan to write and submit the article for the second aim (TRUST depression substudy). We also plan to submit the article on Levothyroxine use in Switzerland within the first quartile of 2020.

Timetable:

		2017	2018				2019				2020			
		Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Aim 1	Systematic literature research													
	Data request, data preparation													
	Data analyses													
	Writing of manuscript and submission for **1st publication**: "The association between subclinical hypothyroidism and depressive symptoms – an individual participant data analysis."													
Aim 2	Data request, preparation and cleaning													
	Data analyses													
	Writing of manuscript and submission for **2nd publication**: "Impact of thyroxine therapy on depressive symptoms in subclinical hypothyroidism – a randomized controlled trial."													
Additional Project	Writing analysis plan together with SantéSuisse													
	Submission of **3rd publication** (2nd author) "Chronic use of levothyroxine: prevalence and users' characteristics in Switzerland"													
	Writing of PhD Thesis													
	PhD defence													

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